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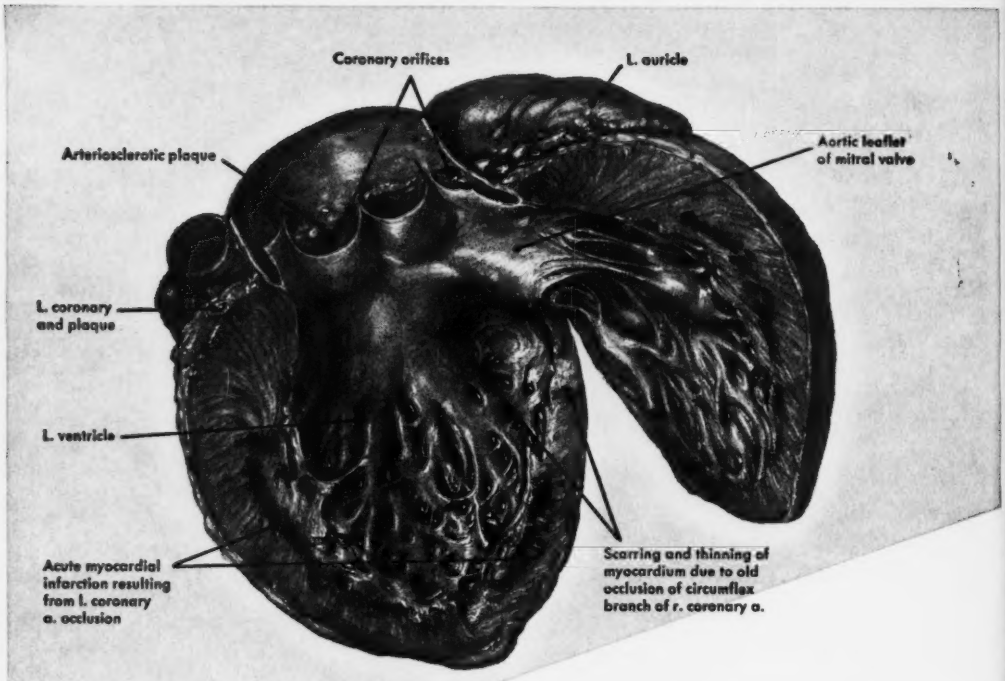

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References:

1. Kurland, G. S., and Malach, Monte: *New England Jour. Med.*, 247:383, Sept. 11, 1952.
2. Sayen, J. J., et al.: *Jour. Clin. Investigation*, 31:658, June, 1952.
3. Gilchrist, A. R.: *Brit. Med. Jour.*, 2:351, Aug. 16, 1952.
4. Miller, A. J., et al.: *J.A.M.A.*, 152:1198, July 25, 1953.
5. Levine, H. D., and Levine, S. A.: *Med. Clin. North America*, 37:955, July, 1953.

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Intermittent Claudication of the Hip and the Syndrome of Chronic Aorto-Iliac Thrombosis

By VICTOR G. DEWOLFE, M.D., FAY A. LEFEVRE, M.D., ALFRED W. HUMPHRIES, M.D., MALIN B. SHAW, M.D., AND GEORGE S. PHALEN, M.D.

It is the purpose of this paper to report the not too widely known clinical symptom of hip claudication and its relationship to aortic and iliac artery occlusions. The importance of aortography in the diagnosis of this syndrome is stressed and a technic is described. The results and findings differ from previous reports in the literature and these variations are discussed.

THE most common symptom of occlusive arterial disease of the lower extremities is intermittent claudication. When present the symptom is pathognomonic of arterial insufficiency. It occurs almost uniformly in patients with arteriosclerosis obliterans and in about 75 per cent of those with thromboangiitis obliterans.[1]

Most authors and clinicians refer to intermittent claudication as pain or fatigue in the calves which occurs after walking a given distance. The discomfort is distressing enough to cause the patient to stop, whereupon, it rapidly subsides in two to five minutes. Following the period of rest, the patient can walk approximately the same distance before the distress again supervenes. The walking distance which incites claudication varies, being decreased by a rapid pace or walking uphill and increased by walking slowly.

Intermittent claudication is not confined to the calf. It is widely known that the distress occasionally will occur in the foot or the thigh. However, it is not widely known that the distress may occur in areas proximal to the thigh, such as the hip, buttock and low back. Descriptions of intermittent claudication in these areas appear rarely in the literature. Consequently, the diagnosis is frequently missed and is most often confused with orthopedic disturbances.

During the last five years 47 patients with intermittent claudication of the hip have been seen at the Cleveland Clinic. A vast majority had not been diagnosed before they were referred to the Clinic, and a significant number were referred as orthopedic problems. Each of the patients was found to have a high arterial occlusion or stenosis involving one or both of the iliac arteries or the lower abdominal aorta.

METHOD OF STUDY

A complete history was obtained and careful physical and vascular examinations were made of each patient. The vascular examination consisted of the following: clinical observation of temperature, color in the horizontal, elevated and dependent positions, trophic changes, and pulsations in the extremities. The only special tests employed were oscillometry, x-ray study of the extremities and pelvis for vascular calcification, and aortography when possible.

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Aortography

Aortography proved invaluable as a diagnostic aid.* It is a relatively simple procedure and has caused little morbidity and no mortality in 170 patients at the Cleveland Clinic. It is now done as an "in and out" procedure under Pentothal anesthesia. Several patients have been subjected to surgery hours to several days after the procedure and only a faint staining of blood has been discernible in the area of the needle puncture. A few patients complained of mild abdominal pain for two to three days following the procedure. By aortography the site and type of occlusion can be definitely located and the collateral circulation delineated. This information is important for prognosis and if surgical intervention is contemplated.

Technic. If the aorta is completely blocked in its terminal portion, a small amount of an opaque medium inserted through a single needle provides sufficient concentration for an excellent aortogram. If, however, the block is a partial one in an iliac vessel, the blood flows rapidly past the injecting needle and more of the opaque medium must be injected per unit of time to provide a concentration sufficient for a distinct, diagnostic roentgenogram. Since it is impossible to ascertain the location and the extent of the block beforehand, we have found that the two needle–two syringe method, which insures a satisfactory film, is preferred in all cases.

The patient is placed in a prone position with blanket rolls under each side of the chest and is lightly anesthetized with Sodium Pentothal administered by arm vein. Unless the aorta is suspected to be to the right of the midline, the left side of the patient is prepared with antiseptic from the midline to the flank and from the tenth dorsal vertebra to the gluteal cleft. This area is blocked off with sterile drapes. An 18-gauge, six-inch needle with stylet is inserted through the skin, four finger-breadths lateral to the midline at the desired level. Since less of the opaque medium is lost if the needles are inserted just below the renal arteries, the level of the second or third lumbar vertebra is used unless contraindicated. The needle is carried down to the lateral wall of the vertebral body which is grazed, as in doing a lumbar paravertebral block. It is inserted one to one and one-half inches farther until the aortic wall is punctured. A definite sensation is felt when the aortic wall is penetrated, analogous to that which accompanies penetration of the dura in a spinal puncture. When the stylet is withdrawn, there is a brisk flow of bright red blood which is not pulsatile unless the patient is hypertensive or the needle is located just above a block. A second needle is inserted one-half inch proximal or distal to the first, parallel to it, and to the same depth. When the stylet of the second needle is withdrawn, a similar flow of blood occurs. We believe that the use of a second needle is a safeguard against insertion of one needle into a renal artery, the celiac axis, or the mesenteric artery. If a free flow of blood is not obtained with the second needle in the same position and at the same depth as the first, both needles are withdrawn and new punctures are made. If doubt still remains, a test exposure with a small amount of opaque medium is obtained.

After the needles are placed in the correct position, Luer-Lok adapters connected to 8 to 10 inches of polyvinyl tubing are attached to each. Two 10 cc. Luer-Lok syringes, each overloaded with approximately 12 cc. of the opaque medium, are attached to the tubing, again by means of Luer-Lok adapters. The syringes are clipped to a slide holder which allows more rapid injection than the former method of holding one syringe in each hand. The anesthetist then injects 5 cc. of Pentothal. Sixty seconds later the opaque medium is injected, the syringes being emptied as rapidly as possible. A total of 24 cc. of 70 per cent Urokon is used. The exposure is started just before the plungers reach the bottom of the barrel and continued after the injection is completed. We believe that this specified length of exposure is extremely important. Unless the opaque medium is in the aorta at the level of the needle tips, it is impossible to know whether the empty area below the needles and above the top of the dye column represents a block, or merely a region through which all of the opaque medium has passed before the exposure was made.

The patient lies on an ordinary operating table at standard height in a fully equipped operating room. A portable Bucky, holding a standard 14 by 17 film, is placed under his abdomen. A 60 milliampere portable x-ray machine which provides a 32 inch tube-to-film distance is used. The average exposure is 0.5 second at 80 kilovolts.

Because it is occasionally necessary to obtain an additional aortogram, the needles are maintained in place until the film is developed, unless there are anesthesia difficulties. It is sometimes desirable to repeat the procedure in the case of a terminal aortic block with only moderate collaterals, with tourniquets on both of the patient's legs, to show the collaterals more clearly.

Results

All of the patients had a history of intermittent claudication and showed definite signs of arterial insufficiency. The symptoms and

* Aortography is not indispensable, and an accurate diagnosis of the syndrome can be made by a careful history and physical examination aided by oscillometry. However, aortography is necessary to distinguish between occlusion of the aorta and both common iliac arteries.

TABLE 2.—*Incidence in Sexes*

Sex	Frequency	%
Men	42	89.4
Women	5	10.6
Total	47	100

TABLE 3.—*Incidence in Age Groups*

Age, Range (Years)	Frequency	%
30–39	2	4.3
40–49	12	25.5
50–59	18	38.3
60–69	14	29.8
70 or over	1	2.1
Total	47	100
Mean age	54.4 years	

findings are tabulated in table 1.* The sex distribution (table 2) indicates that the syndrome primarily affects men; 42 of the 47 patients (89.4 per cent) were men. A most striking feature of the study was the comparatively young age at which the patients were afflicted (table 3). Of the 47, only 14 patients (29.8 per cent) were 60 years of age or older; 18 (38.3 per cent) were in the sixth decade; 12 (25.5 per cent) were in the fifth decade; and 2 (4.3 per cent) were in the fourth decade. Thirty-two (68 per cent) of the patients were less than 60 years of age. The mean age for all patients was 54.4 years.

The location of the pain or distress in the group studied is tabulated in table 4. The outstanding symptom was intermittent claudication of the hip, a prominent complaint of all of the patients except five; one of these complained only of weakness of the entire lower extremity, and the other four of distress in the thighs, low back, and abdomen. Thus 46 (97.8 per cent) of the 47 patients had symptoms at a high level, that is, in the hips, thighs, low back or abdomen. As noted in table 4, 26 patients (55.3 per cent) had no symptoms referable to the calf or any part of the leg. Not one patient had distress in the calves alone. In many cases this led to difficulty in making a diagnosis or to a mistaken diagnosis. It may be concluded that occlusion of the terminal aorta or iliac vessels causes intermittent claudication of the hip with frequent radiation to the low back, thigh, and leg. Rarely does it cause distress in the low abdomen.

* At the request of the Editor table 1 is being omitted. This table will be furnished on request with the reprints.

TABLE 4.—*Site of Intermittent Claudication*

		%
Hips and/or location proximal to calves	26	55.3
Hips only	13	
Hips *plus* thigh and low back	11	
Thigh and low back only	2	
Calves *plus* location proximal to calves	20	42.5
Calves only	0	
Calves and hips	6	
Calves, hips and other high location	12	
Calves, thigh, low back, and abdomen	2	
Weakness of entire extremity	1	2.2
Total	47	100

Summary

Number of patients with distress in hips	42	89.4
Number of patients with distress in locations other than hips	5	10.6
Total	47	100

Another striking feature of the syndrome is that the nutrition of the legs and feet is almost always good (table 5). The presence of trophic changes is unusual. Thirty-four of the 47 cases had good nutrition, and eight fair nutrition. Only five had poor nutrition or definite trophic changes. Thus 42 or 89.4 per cent had adequate nutrition. It is interesting that three of the five patients with poor nutrition had occlusion of the external iliac artery. The other two patients had evidence of more peripheral involvement of the arteries in the lower extremities. None of the patients with occlusion of the aorta or common iliac arteries had poor nutrition. It appears that the higher (or more proximal) occlusions are more apt to be associated with an efficient and adequate collateral circulation. This conclusion is confirmed by the findings on aortography.

Findings on Aortography. Thirty of the 47

TABLE 5.—*Nutrition of Feet or Legs*

	Frequency	%
Good	34	72.4
Fair	8	17.0
Poor	5	10.6
Total	47	100

TABLE 6.—*Diagnosis by Aortography*

Location of Block	Frequency	%
Occlusion of abdominal aorta	7	23.3
Occlusion of one common iliac artery	11	36.7
Occlusion of both common iliac arteries	4	13.3
Occlusion of one external iliac artery	2	6.7
Occlusion of one common iliac artery and the opposite external iliac artery	1	3.3
Diffuse involvement of aorta and iliac arteries	1	3.4
Unsatisfactory or not diagnostic	4	13.3
Total	30	100

patients were studied by aortography and the findings are summarized in table 6. It is at once apparent that the commonest site of occlusion was in one of the common iliac arteries. Seven cases had blocks in the terminal aorta varying in location from just below the renal arteries (three cases) to the bifurcation. Four patients had both common iliac arteries involved and clinically these patients were indistinguishable from those with aortic occlusions. Therefore, in this group the aortogram was particularly valuable because the prognosis may be considerably more grave when the aorta is involved. The common iliac artery was involved in combination with the opposite external iliac artery in one case. The common iliac artery was implicated in 16 of the 30 cases (53.3 per cent).

The discussion of the various anastomotic channels utilized in aortoiliac occlusion is intended to be the subject of a later paper. However, there are two principal routes which appear to be most common. One is

TABLE 7.—*Calcification by X-ray*

		%
Present	19	40.4
Av. age, 54.9		
Absent	26	55.3
Av. age, 52.4		
No x-rays	2	4.3
Total	47	100

more laterally placed, consisting of blood from the lumbar arteries passing to and through the "cruciate circulation" of the hip and returning to the femoral artery or arteries via the medial and lateral circumflex femoral arteries. The ascending branches of the medial and lateral circumflex arteries may or may not enter into this system.

Of lesser import and frequency, and seen in the lower occlusions (iliac) is a more medially placed anastomosis from the lower lumbar and/or upper sacral arteries, through the obturator artery, to the circumflex femoral arteries and thence to the femoral. Depending on the site of the block, the superior and inferior gluteal vessels and the deep circumflex iliac artery may enter into this system.

Findings on Simple X-ray Study. In contrast to aortography, plain x-ray films were not too helpful (table 7). Calcification of the aorta or pelvic vessels was present in only 19 and absent in 26 of the 45 patients who were roentgenographically studied. When calcification was present it was merely confirmatory and did not necessarily correspond to the site of the occlusion as demonstrated by the aortogram. The calcification was never of the Mönckeberg type.

Pathologic Findings. Pathologic material was available in only four cases (cases 6, 10, 11 and 18, table 1*). Case 6 had resection of the terminal aorta and a portion of both common iliac arteries and cases 10, 11 and 18 had endarterectomies performed. Case 11 died and a complete autopsy was performed. The pathologic findings were essentially those of arteriosclerosis in each case. The thrombi were

* See footnote on page 3.

well organized. In case 6 there was extreme chronic inflammation of the aortic wall.

Differential Diagnosis

Because the syndrome of insidious thrombosis of the terminal aorta and iliac arteries is not widely known, a mistaken diagnosis is common. In our experience recognition of an embolus or an acute thrombosis has presented no problem and has never been mistaken for this syndrome. It is conceivable that a patient who has recovered from an embolus to the terminal aorta or an iliac artery might present himself with the signs and symptoms of this syndrome, but we have never encountered such a situation. On the other hand a large number of the group studied were diagnosed as orthopedic problems such as ruptured intervertebral disks, osteoarthritis of the lumbosacral spine or hip, or bursitis of the hip.

True intermittent claudication of the hip area can be produced only by some pathologic condition which reduces the vascular supply to the musculature about the hip. Various orthopedic and neurosurgical conditions must be considered. These conditions may be readily differentiated if the examining physician will remember to check the status of the arterial circulation in the lower extremities of every patient complaining of pain in the low back, hip, thigh and leg. A careful history will then enable him to decide whether or not there is a true intermittent claudication of the hip.

Hypertrophic arthritis of the hip is a common cause of pain in the hip of patients more than 50 years of age. The patients complain of pain in the muscles about the hip which is aggravated by activity and relieved by rest. The rest must be prolonged and the patient prefers to sit down. Some restriction of movement in the hip joint always accompanies the pain, and roentgenograms reveal the typical cystic and sclerotic changes involving the acetabulum and the head of the femur. Although there may be evidence of some arteriosclerosis of the vessels of the involved extremity, there is usually no evidence of severe impairment of the arterial circulation.

A localized fibrositis or a simple, nonsuppurative bursitis is the most common cause of pain in the hips of patients less than 50 years of age. In cases of bursitis, there is exquisite tenderness immediately over or adjacent to the bursa, and passive movement of the hip joint usually aggravates the pain. In cases of fibrositis, there are frequently "trigger points" or areas of extreme tenderness either in the muscle bellies or at the tendinous attachments of muscles to bone. Local infiltration of these tender areas with a dilute solution of Novocain will usually give immediate relief from pain.

A protruded intervertebral disk in the lower lumbar region may simulate a true intermittent claudication of the hip. It is true that any pressure or irritation of the fifth lumbar or first sacral nerve root may produce pain in the posterior hip area, radiating down the leg in the course of the sciatic nerve. The pain due to a protruded disk is almost always aggravated by bending, lifting, coughing or straining. In contradistinction to intermittent claudication of the hip, the pain associated with a protruded disk is not necessarily dependent upon movement for its production or aggravation. A protruded disk usually produces some alteration in the deep tendon reflexes in the involved extremity and occasionally produces characteristic sensory changes and muscular weakness in the leg.

All malformations and diseases involving the structures about the hip may be accompanied by some intermittent pain in this area. The restriction of passive movement in the hip by muscle spasm, bony abnormality or incomplete fibrous ankylosis, and the presence of an adequate arterial circulation in the lower extremity serve to differentiate these conditions readily from true intermittent claudication of the hip.

Treatment

The treatment of thrombosis of the terminal aorta and iliac arteries is far from satisfactory. Ideally, as recognized by many, the treatment of choice is complete excision and replacement by graft, whether an autogenous or homologous artery or vein, or an artificial channel of some sort. As yet this is in its infancy although definite strides are being made. Freeman and

Leeds[2] have reported the use of autogenous vein grafts, using either the left iliac or right jugular vein in three patients, two of whom had abdominal aneurysms and one, thrombosis of the terminal aorta. The latter patient survived the procedure but only an immediate postoperative follow-up was possible because of the recent surgery. Oudot[3] reported successful arterial grafting of the aortic bifurcation in a patient with thrombosis. The successful use of arterial homografts and autografts in dogs' aortas was reported by Parsons, Gerbode and Cox.[4] They found, however, that those with autografts tend to survive while those with homografts do not, although the aortas remain patent. Julian and co-workers[5] reported success in three cases of thrombosis of the terminal aorta replaced by quick-frozen preserved aortic bifurcations. Finally, Gross and his co-workers[6, 7] have had notable success with the use of grafts in the thoracic aorta.

Endarterectomy which involves various methods of opening the artery and removing the thrombosis along with the intimal lining and perhaps some of the media has only a few advocates.[5, 8-11] Following removal of the thrombus the vessel lumen remains patent in only a small percentage of patients and the procedure has been abandoned by many surgeons in the field of vascular surgery. It has not been successful in our hands.

Leriche[12, 13] in his classic description of thrombosis of the terminal aorta recommended resection of the involved portion of the aorta and iliac arteries and bilateral lumbar sympathectomy. He stated that removal of the thrombus would prevent its propagation either proximally or distally and would also remove the "arterioarterial vasoconstrictor reflexes" which arise within the vessel wall. This procedure has been recommended by many others.[14-22]

Table 8 summarizes the results of treatment in our 47 cases. Unilateral sympathectomy was done in seven cases but the results were unimpressive; three patients improved and four patients remained unchanged. Of seven cases submitted to bilateral sympathectomy, six were improved. In this entire group the first lumbar ganglion was removed as well as the lower segments when possible. However, the improvement was not spectacular and in general amounted to a doubling or tripling of the distance the patient was able to walk before intermittent claudication occurred. In two cases pain was relieved, but in its stead fatigability appeared which was almost as incapacitating as the pain. In general, however, this group has improved during a follow-up period of six months to one and one-half years.

TABLE 8.—*Treatment*

Sympathectomy only		14
Unilateral	7	
Improved	3	
Unimproved	4	
Bilateral	7	
Improved	6	
Unimproved	1	
Endarterectomy only		1
Improved	0	
Unimproved (amputation)	1	
Endarterectomy plus bilateral sympathectomy		2
Improved	1	
Unimproved (died)	1	
Resection of aorta and iliac arteries plus bilateral sympathectomy		1
Improved	1	
Conservative treatment		29
Improved	11	
Unimproved	10	
Worse	3	
No follow-up	5	
Total		47

Our experience with definitive surgery has been meager but impressive enough to lead us to the conclusion that conservative treatment should be used until more successful methods of treatment are worked out.

Our experience with conservative treatment has been enlightening. As noted in table 8, 29 patients have been placed on the following program of treatment: Smoking is forbidden; the patient is allowed to walk as much as he desires but is instructed to walk slowly and stop at the first sign of distress; he is told to elevate the head of the bed four to six inches on blocks; and is instructed in care of the feet. Frequently reflex heat to the abdomen for 20 minutes twice a day is used.

During a five-year period only three of the

29 patients became worse. One of these died of "Bright's disease" as reported in a letter from his wife (case 20, table 1*). The two others (cases 19 and 45, table 1*) have had mild progression of their disease. The claudication distance of one (case 45, table 1*) has decreased from two blocks to one block during the five-year period. The other had diffuse disease as demonstrated on the aortogram (case 19, table 1*). There has been no follow-up in five cases.

Of the remaining patients, 11 have improved and 10 have remained unchanged. This entire group is getting along well. They are inconvenienced by intermittent claudication but are leading lives as useful citizens. This seems to indicate that this syndrome is not a chronically progressive one which inevitably terminates in gangrene or death as reported by others.[12, 14, 15, 19, 20] Leriche[12] suggests that the process begins in the iliac arteries and progresses to involve the terminal aorta. Admittedly we have not followed these patients for a prolonged period of time on conservative treatment (table 9) and only two patients have been followed for five years. However, a more impressive number (13 cases) have been followed for two and three years. It is possible that the disease is chronically progressive over a greater period of years but as yet we have no indication of it. No long term studies have been published confirming the assertion that gangrene invariably follows or that death occurs due to involvement of the renal arteries. Our patient (case 20, table 1*) who died of Bright's disease conceivably died of this cause, but unfortunately an aortogram was not done and we have no reliable follow-up information on the case.

In view of the preceding facts we offer the following statement in regard to treatment: With the uncertain methods presently at our disposal, conservative treatment and close follow-up observations appear to be the treatment of choice until such time as resection and grafting become practical and safe. Bilateral lumbar sympathectomy including the ganglia of L-1, if possible, can be employed in those cases which have definite trophic changes or incapacitating symptoms. The degree of relief from this procedure, however, should not be expected to be great.

TABLE 9.—*Conservative Treatment*

Length of Follow-up*	Improved	Unimproved	Worse
Less than 1 yr.....	2	1	0
1 yr.....	3	2	1 (died)
2 yrs.....	4	3	1
3 yrs.....	2	3	0
4 yrs.....	0	0	0
5 yrs.....	0	1	1
Total.....	11	10	3

* No follow-up, 5.

REPORT OF CASES

The following are six representative cases chosen from the group of patients who had aortograms in order to demonstrate the pathology. On the basis of the preceding discussion, the surgical treatment employed in some of the cases is not necessarily recommended.

Case 1. (table 1,* case 2) E. B., a 53 year old businessman, was first seen at the Clinic on Dec. 6, 1950, complaining of weakness and "numbness" in the sacral area of eight months duration. The initial symptoms had occurred two to three years previously on hunting trips and consisted of pain and numbness in the calves of the legs during walking which were relieved by stopping for a short period. The symptoms progressed and at the time he was first seen the distress occurred in the small of the back with radiation to the lower abdomen on walking three blocks. At the same time a coldness and numbness occurred in the legs and feet. These symptoms were relieved by a few minutes rest.

Physical examination showed the temperature to be normal, pulse 72, and blood pressure 130/80. The positive findings were limited to the lower extremities. Both feet were cold. There was pallor on elevation and rubor on dependency, especially on the left. Faint right femoral and bilateral posterior tibial pulses were present; the other pulses were absent. The venous filling time was normal. The examination of the heart was negative. Routine laboratory studies were normal. The blood cholesterol was 273 mg. per 100 cc. X-ray films of the chest and pelvis were negative. The electrocardiogram was normal.

* See footnote on page 3.

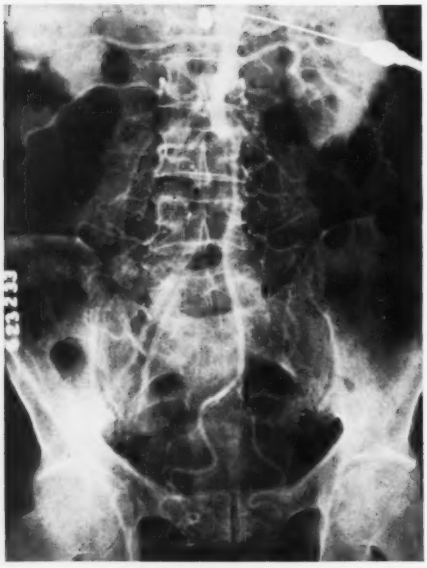

FIG. 1. (Case 1 or table 1,* case 2, E. B.) Complete block terminal aorta just below the third lumbar arteries. Faint filling of the iliac arteries on both sides. Collateral circulation is from the lumbar arteries through the iliolumbar and superior gluteal arteries.

An aortogram (fig. 1), which was obtained on April 2, 1951, four months after the initial examination, showed a complete block of the abdominal aorta at the level of the third lumbar vertebra with narrowing for 6 cm. above.

Left paravertebral lumbar sympathetic blocks produced considerable subjective but no objective warming of the left lower extremity. A left lumbar sympathectomy was performed on April 5, 1951. He was last heard from 13 months later when he reported a gradual improvement of symptoms. The pain had disappeared but he experienced fatigue on walking.

Case 2. (table 1,* case 3) C. S., a 49 year old businessman, was seen at the Clinic on July 27, 1949, complaining of aching in the hips and low back brought on by walking two blocks and relieved by rest. Physical examination was not remarkable. The blood pressure was 126/86. The lower extremities had good pulsations at all levels and there were no physical signs of arterial insufficiency.

X-ray films of the lumbosacral spine showed calcifications believed to be in the abdominal aorta and the pelvic vessels. There were hypertrophic bone changes. It was believed by the examiner that the patient's symptoms were due to degenerative joint disease.

The patient returned two years later on Sept. 18, 1951. The symptoms had progressed somewhat in severity. After one block of walking the pain started in the hips and buttocks and progressed into the legs and feet. The feet were always cold and occasionally became numb with exercise. There was no impotency.

Physical examination showed the temperature and pulse to be normal. The blood pressure was 150/95. There were asthmatic wheezes in the lungs. Examination of the lower extremities revealed the temperature and nutrition of the feet to be good. There was moderate pallor on elevation and rubor on dependency. The venous filling time was 30 seconds bilaterally. All pulses were absent except an extremely weak right femoral pulse. Oscillometric readings showed only faint pulsations in the thighs. X-ray films of the pelvis again revealed aortic and pelvic calcifications. The chest x-ray films were negative. Routine laboratory studies were normal.

An aortogram (fig. 2) showed complete obstruction of the aorta just below the level of the renal arteries. The origin of the left renal artery appeared to be slightly narrowed. He was placed on conservative medical management and has had no change in his symptoms over a period of one and one-half years.

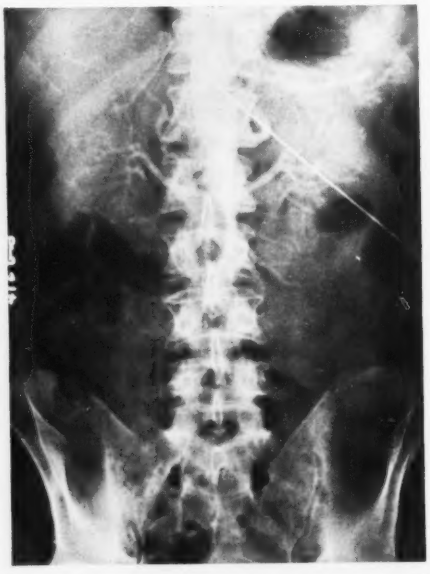

FIG. 2. (Case 2 or table 1,* case 3, C. S.) Complete block of aorta below the renal arteries. Collateral circulation not demonstrated by the one-needle technic.

* See footnote on page 3.

Case 3. (table 1,* case 10) L. S., a 62 year old man, a laborer, was first seen on Jan. 29, 1953, with a complaint of pain in the right hip and buttock of three months duration. The pain occurred suddenly one day while walking and caused him to stop, whereupon it subsided within two minutes. It occurred occasionally on prolonged standing and at night when lying on the opposite side. As time went on he noticed in addition to the hip pain, a weakness in the leg and a numbness down the posterior aspect of the thigh, calf and lateral aspect of the foot. The pain was not aggravated by coughing or straining or by motions of the back.

After roentgenographic examination, he was told he had osteoarthritis of the spine. In December 1952 he saw a neurosurgeon who noticed slight atrophy of the right gluteus muscle and a diminished right angle jerk. A diagnosis was made of osteoarthritis of the spine with nerve root compression at the level of the first sacral segment owing to a spur or a possible ruptured intervertebral disk. The patient was hospitalized for study. The spinal fluid was negative. Two diskograms were obtained in December and January and these showed degenerated disks between the fourth and fifth lumbar vertebrae and the fourth lumbar and first sacral segment, but no protrusion. The pain was not reproduced. A myelogram was negative.

There was no history of diabetes or heart disease.

Physical examination showed a well-developed and well-nourished man of 62 years. Blood pressure was 190/100 which later fell to normal. A complete examination was noncontributory except for the findings in the lower extremities. There was good nutrition of both feet which were warm and of healthy color. On elevation of the extremities moderate pallor of the right foot occurred and on dependency slight rubor. The venous filling time was normal. The peripheral pulses on the left were present and full. On the right only a faint femoral pulsation was felt. Oscillometric examination was normal on the left but abnormal on the right, showing absence of pulsations except for a faint deflection in the thigh.

Laboratory studies including red and white blood cell counts, hemoglobin content, blood sugar and serology were negative. X-ray films of the chest and pelvis were negative. There was no evidence of calcification of the pelvic arteries. An electrocardiogram was not obtained.

An aortogram (fig. 3) done on Jan. 29, 1953, showed occlusion of the right common iliac artery at its origin. There was excellent collateral circulation through the fourth lumbar artery with refilling of the common iliac artery below the block just above the level of the bifurcation into external and internal iliac arteries. There was moderate narrowing of the external iliac artery and slight irregularity of the terminal aorta. The visualization on the left was normal except for some irregularity of the common iliac artery.

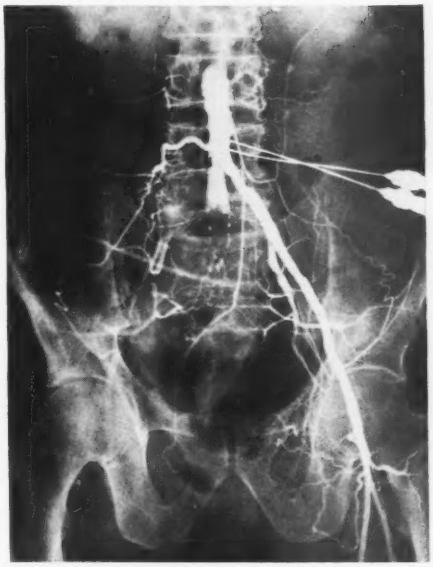

FIG. 3. (Case 3 or table 1,* case 10, L. S.) Complete block of right common iliac artery with some narrowing of the left. Faint filling of the right external iliac is seen. Most of the collateral circulation is through the anomalous fourth lumbar artery through the iliolumbar artery and the deep circumflex iliac artery.

On Jan. 30, 1953, a bilateral lumbar sympathectomy from L-1 to L-4 and endarterectomy of the thrombus in the right common iliac artery were done. The patient made an uneventful postoperative recovery, but there was no change in the pulses.

The patient was seen on March 25, 1953, approximately two months postoperatively, and he stated that he no longer had pain on walking but had some fatigue in the right thigh after one block of walking, but that this was improving. He estimated his improvement to be 75 per cent. The extremity was warm but the pulses and oscillometric readings were unchanged.

Case 4. (table 1,* case 7) C. R., a 48 year old man, a merchant, was seen at the Clinic in January 1953, complaining of an aching pain in the hips and buttocks of two years duration. He had no difficulty walking around in his store and spent long hours on his feet, seven days a week, without difficulty. However, continuous walking out of doors produced the

* See footnote on page 3.

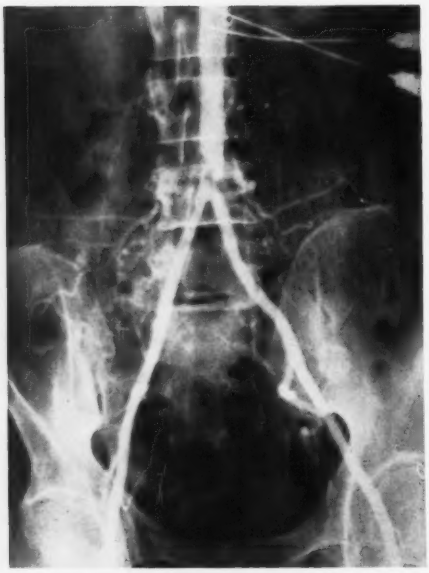

FIG. 4. (Case 4 or table 1,* case 7, C. R.) Incomplete block of the terminal aorta with relatively little collateral circulation.

pain after five or six blocks of slow walking or one block of rapid or upgrade walking. The distress started mildly in the calves but quickly involved the hips and buttocks where it was severe enough to make him stop. Resting relieved the pain in one minute or less. He could then walk the same distance before the distress recurred. There had been no progression of the symptoms. He complained of slight coldness of his feet. He had no difficulty with penile erections. He had been a heavy smoker but had stopped one year previously.

Physical examination showed his temperature to be 98.8 F. by mouth, pulse 88 and blood pressure 150/88. He was well-nourished and well-developed. The examination was essentially normal except for the lower extremities. The temperature, color and nutrition of the feet and legs were excellent. There was no evidence of muscular atrophy. Mild pallor was produced on prolonged elevation. There was no rubor on dependency. The venous filling time was normal. Examination of the pulses revealed the following based on 0 (no pulses) to 4 (strong pulses): right femoral 2, right popliteal 1, right posterior tibial 1, right dorsalis pedis 2; left femoral 1, left popliteal 0, left posterior tibial 1, and left dorsalis pedis 2. On exercise to the point of pain the pulses disappeared. Oscillometric readings were within normal limits at all levels in both lower extremities.

Laboratory studies which included a blood count, urinalysis, blood sugar and serology were negative. The cholesterol was 254 mg. per 100 cc. The electrocardiogram was not diagnostic. The chest x-ray films were negative. The plain film of the pelvis showed no vascular calcifications.

The aortogram (fig. 4) showed a filling defect in the terminal aorta just above the bifurcation. The defect was oblique in direction and irregular in shape but apparently it was not a complete block because of excellent filling of the terminal aorta and both iliac vessels.

The patient was treated conservatively because of the rather good arterial circulation at rest and during a period of six months there has been no change in symptoms.

Case 5. (table 1,* case 6) P. T., a 47 year old salesman, was seen at the Clinic on Nov. 13, 1952, complaining of severe fatigue of both lower extremities after walking two blocks slowly, one block rapidly or one flight of stairs. The symptoms had begun one year prior to examination and seemed to become progressively worse. The distress began in the hips and thighs and quickly involved the calves. One or two minutes' rest rapidly relieved the discomfort. The patient was nervous, tense, preoccupied and the history was difficult to obtain. He smoked two packages of cigarettes a day. It was difficult to get a reliable history regarding potency. He stated he had a decreased desire, but he was able to have an erection and ejaculation. The patient's wife denied that her husband had any sexual difficulties. When the patient was seen again three weeks later, his wife stated that during the period since the previous interview her husband had been unable to maintain a penile erection. It was concluded that this difficulty may well have been psychogenic in origin.

Physical examination showed a temperature of 98.4 F. by mouth, pulse 88 and blood pressure 124/86. The patient was well-nourished and well-developed but appeared older than his stated age of 47 years. The significant findings were limited to the lower extremities. Both feet were cool but showed excellent nutrition. Hair and nail growth were normal. There was moderate pallor on elevation which was delayed three to four minutes in both feet. On dependency the color returned in mottled fashion and the final result was a moderate rubor. The venous filling time was 35 to 40 seconds. All pulses were absent except a faint pulsation in the right femoral area. The aorta was felt as a strong pulsation just below the umbilicus. There was no bruit.

Laboratory studies showed the blood cell count, urinalysis, fasting and two and one-half hour blood sugars, and tests for syphilis to be normal. The blood cholesterol was 227 mg. per 100 cc. The electrocardiogram was normal.

The chest x-ray films were negative. X-ray study

* See footnote on page 3.

of the pelvis showed faint calcification opposite the third lumbar vertebra on the lateral film which was believed to be in the aorta. The antero-posterior film showed small vascular calcifications below the left sacroiliac joint.

The aortogram (fig. 5) showed irregularity and slight narrowing of the terminal aorta. There was partial occlusion at the bifurcation with a complete occlusion of the right common iliac artery and partial occlusion and extreme narrowing of the left common iliac artery. There appeared to be fair collateral circulation through the third and fourth lumbar arteries which were enlarged.

The patient was hospitalized and subjected to the operation suggested by Leriche. The terminal aorta was resected proximally to a level just below the large fourth lumbar artery together with the proximal portions of both common iliac arteries. The thrombosed segment was completely removed, but definite atheromatous changes were present in the aorta above the resected segment. A bilateral lumbar sympathectomy from L-1 to L-5 was done at the same time.

The pathologic report stated that the left common iliac artery was occluded by an old thrombus mottled yellow and gray in color. The right common iliac and terminal aorta appeared to be occluded by recent thrombus mottled red and faint gray in color. The walls of all the vessels were moderately thickened by arteriosclerosis. The microscopic changes were typical of atherosclerosis. There was marked chronic inflammation of the aortic wall.

The patient made an uneventful recovery, but although the legs were warmer, there was no change in the patient's symptoms.

A follow-up aortogram, taken on July 31, 1953, revealed no evidence of proximal propagation of the disease. The symptoms were unchanged.

Case 6. (table 1,* case 31) R. R., a 47 year old man, an industrial worker, was seen in Feb. 1953 complaining of pain in the calves, hips, buttocks and low back after walking one block. The symptoms had begun eight months before examination when he had experienced a tightness and extreme tiredness of his calf muscles while he was mowing the lawn. This was relieved completely by resting for one minute. However, from that time on the discomfort recurred with extension into the hips, buttocks and low back whenever he walked the equivalent of one city block. He obtained relief by resting two minutes. The distress was more severe on the right. He experienced no rest pain, coldness or numbness and noticed no color changes in the feet.

The system review was negative. There was no history of rheumatic fever. He had served in the Armed Forces and had received an honorable discharge. He denied any difficulty with penile erections.

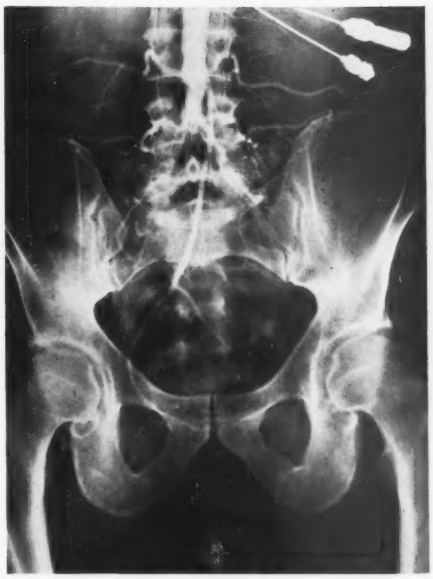

FIG. 5. (Case 5 or table 1,* case 6, P. T.) Complete block of the right common iliac artery and questionably complete block of the left common iliac artery. There is very faint filling of both external iliac arteries seen within the pelvis.

Physical examination revealed a well-nourished and well-developed man in no distress. The temperature was 99.2 F. by mouth, pulse 80 and blood pressure 140/90. The heart was slightly enlarged to the left. There was a normal sinus rhythm. A grade 3 systolic murmur was heard at the apex and a soft blowing diastolic murmur was heard along the left sternal border and in the aortic area. These findings were interpreted as being due to rheumatic heart disease with mitral insufficiency and aortic insufficiency, class IA. The lungs were clear.

The lower extremities were small and the buttocks appeared to lack normal muscle mass. The patient stated, however, that he had had small legs all of his life. The lower extremities showed good nutrition, but were cool throughout. There was extreme pallor on elevation but normal color on dependency. All the pulses in both lower extremities were absent except for a faint pulsation in the right femoral area.

Laboratory studies including a white blood cell count, hemoglobin content, urinalysis, fasting blood sugar and urea were normal. The serology was negative. The electrocardiogram showed no diagnostic changes. X-ray films of the chest with cardiac tech-

* See footnote on page 3.

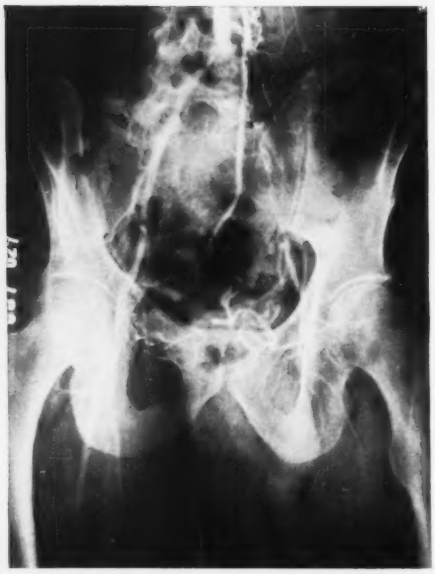

FIG. 6. (Case 6 or table 1,* case 31, R. R.) Complete block of the left common iliac artery with refilling of the external iliac artery at a lower level. There is almost complete stenosis of the right common iliac artery.

nic showed a normal configuration with 13 per cent enlargement by the Ungerleider scale. The lung fields were clear.

The aortogram (fig. 6) showed narrowing of the terminal aorta with a complete block of the left common iliac artery and a partial block of the right common iliac artery. There was excellent collateral circulation on the left.

On Feb. 25, 1953, a bilateral lumbar sympathectomy including L-1 as well as the lower ganglia was performed. The patient made a rapid recovery postoperatively and at the time of discharge was able to walk approximately two city blocks rapidly without discomfort. The patient has not returned for follow-up examination.

DISCUSSION

Prior to Leriche's classic description of thrombotic occlusion of the terminal aorta in 1940,[12, 13] sporadic descriptions of the condition had appeared in the literature. The literature has been frequently reviewed.[14-18, 23, 24] Most of the earlier cases were due to embolism or acute thrombosis, and the syndrome of chronic insidious thrombosis of the terminal aorta was not made clear. Leriche stated that the typical symptom complex occurred in young adult men in the third to sixth decades. They complained of inability to maintain a penile erection and extreme fatigue and weakness of both lower extremities on walking. He stressed that this was not intermittent claudication. Examination showed global atrophy of both lower limbs, absent pulses, pallor of the legs and feet even when standing, and the absence of trophic changes. Since this description an increasing number of cases has been reported in the literature. There is no agreement that the syndrome produces a picture as characteristic as Leriche describes, but all the authors have observed one or more of the previously mentioned clinical features. Holden[25] in 1946 reported the cases of two patients who suffered from impotence, intermittent claudication, extreme fatigability of the lower extremities and atrophy of the thighs and legs. All 10 patients reported by Elkin and Cooper[15] had intermittent claudication; 7 had easy fatigability on walking, 3 had impotence, and only 1 had atrophy. Milanes, Perez-Stable and Lastra[19] reported 13 cases in 1950; 12 of these patients had intermittent claudication, 2 fatigability, 7 impotence and 9 atrophy of the lower extremities. All three of Ortner and Griswold's[14] patients had intermittent claudication; one had loss of penile erections, and two had atrophy. Boyd's[20] two patients had intermittent claudication, fatigability, and inability to maintain an erection, and one had atrophy of both lower extremities. All four patients cited by Elliott and Peck[21] had intermittent claudication and one had loss of erections. They did not mention fatigability or atrophy.

It is apparent then that intermittent claudication is a constant symptom which occurs in practically all cases of thrombosis of the terminal aorta in contrast to Leriche's description. On the other hand, a significant but variable number of patients experience fatigability without pain, loss of potency or atrophy of the lower extremities. Some authors[17, 22, 24, 26-28] mention intermittent claudication or fatigue but make no mention of

* See footnote on page 3.

potency, pallor on dependency or atrophy. Goodwin and Petrie[29] report a patient who had neither intermittent claudication nor fatigue but showed the buttocks and lower limbs to be lacking in muscle mass.

Descriptions of the clinical picture of thrombosis of one or both of the common iliac arteries are exceedingly rare in the literature. This is surprising inasmuch as it is approximately seven times as frequent in occurrence as thrombosis of the terminal aorta in our experience. In addition Leriche and others have stated that thrombosis of the iliac arteries is the first step in the pathogenesis of thrombosis of the aorta. If this were so, thrombosis of the iliac artery would be seen more frequently or at least as frequently as thrombosis of the terminal aorta. Kekwick, McDonald and Semple[30] in 1952 reported that 8 out of 53 consecutive cases of intermittent claudication had arterial obstruction above the inguinal ligament. In one of these the obstruction involved the aorta and in seven the iliac arteries. All of the patients had intermittent claudication. None complained of weakness and/or inability to maintain an erection. Four patients showed trophic changes, two having ulcers and one gangrene. It is not made clear whether the common or external iliac arteries were involved in these cases. They described definite wasting and hypotonia of the buttocks on the affected side in six of the seven cases of proved iliac artery obstruction. We have not been impressed with this finding although we have looked for it. It is interesting that these authors treated six cases conservatively and none deteriorated while two improved.

In 1950 Boyd and Jepson[31] described two cases of thrombosis of the external iliac artery and stated that a search of the literature produced no description of such a lesion and its sequelae. Both cases were young men with symptoms of sudden onset following trauma. Lindbom[32] reported six cases of occlusion of the iliac artery out of 76 patients with arteriosclerosis obliterans. No description of the typical syndrome of common or external iliac artery thrombosis could be found in the literature.

We have reported the clinical picture of 47 cases and aortography findings of 30 cases of occlusion of the terminal portion of the aorta or one or both of the common iliac arteries. We have not been impressed with all the tenets set forth by Leriche. Only rarely did we encounter such symptoms and signs as inability to maintain a stable penile erection (definitely in case 5, table 1,* only), fatigability without pain (case 11 and case 12, table 1*), and atrophy of the lower extremities (case 5 and possibly case 31, table 1*). We have never observed pallor of the legs or feet in the dependent position. On the other hand, our studies confirm the age incidence and the sex distribution of this syndrome. We were also impressed by the absence of trophic changes.

The occurrence of intermittent claudication at a high level, that is, in the hip and area about the hip, deserves special attention for the following reasons: (1) It is pathognomonic of an arterial occlusion located above the inguinal ligament; (2) it occurs in almost 100 per cent of such cases; and (3) it is a symptom with which most physicians are not familiar unless they have a special interest in peripheral vascular diseases. Unfortunately, intermittent claudication has become synonymous with pain in the calf on walking. However, it need not be a pain, but may be a cramp, a tightness, a weakness, or a feeling of profound fatigue. It may occur in any muscle which has its blood supply impaired during exercise. It is common in the foot, thigh and hip. It is less common in the hand, forearm, upper arm, low back and lower abdomen. Fatigability which is mentioned by Leriche[13] and many other authors as usually occurring in addition to a pain on exertion in the syndrome of insidious thrombosis of the aorta and not as a solitary symptom, is typical intermittent claudication because it, like the pain, comes on with walking and is quickly relieved by rest.

Few authors have stressed or even mentioned that the intermittent claudication of aortic or common iliac artery thrombosis occurs in

* See footnote on page 3.

the thigh, hip or buttock alone or in association with calf claudication. Allen, Barker and Hines[33] mention in their textbook that the site of intermittent claudication roughly indicates the level of the occlusion, and that when the thighs, hips and lumbar region are affected it indicates an occlusion of the iliac arteries or aorta. Boyd and Jepson,[31] Lindbom,[32] McCombs and associates,[22] Elliott and Peck[21] and Greenfield[17] mention that their patients had pain in the thigh as well as the calf, but the hip was not mentioned. Six of the eight patients reported by Kekwick[30] had claudication of the thigh and one had buttock claudication. Shapiro,[34] Ortner and Griswold,[14] Elkin and Cooper,[15] and Goodwin and Petrie[16] emphasize that the claudication may involve the hip area. Milanes and colleagues[19] describe 13 cases, 9 with occlusion of the aorta and 4 of the iliac arteries, all of which had intermittent claudication, but they do not mention the site of the distress. All of our cases complained of intermittent claudication at a level higher than the calf except for one who complained of weakness of the entire extremity on walking. Therefore, we feel that this symptom occurs almost invariably.

The etiology was believed to be thrombosis secondary to arteriosclerosis in all cases. The process was localized in the vast majority of the cases involving either the terminal aorta, iliac arteries, or both. Exceptions were cases 13, 16, 19, 39, 42 and 43 (table 1*). The remainder of the patients had no signs of generalized arteriosclerosis. They were in a relatively young age group (table 3) and only one patient (case 12, table 1*) had diabetes mellitus. Only four had arteriosclerotic heart disease manifested by angina pectoris or a previous myocardial infarction. The four cases in which pathologic material was available presented the typical findings of arteriosclerosis. It seems likely, then, that the thrombus originates on an ulcerated, atheromatous plaque or less likely from hemorrhage beneath a plaque with obstruction and secondary thrombus formation. There was no history of an acute episode suggestive of an embolus in any of the cases.

In studying these cases several other interesting observations were made. Leriche and others have stated that hypertension, particularly of the systolic type, is a frequent finding. We have been unable to confirm this (table 1*). Only nine patients (average age of 59 years) had a systolic pressure of 160 mm. Hg or above, and only two of these had diastolic pressures of 100 mm. Hg or above. Interestingly enough the seven cases with occlusion of the aorta had the following blood pressures: 136/76, 118/76, 132/92, 124/86, 150/88, 130/80 and 150/95.

We have also analyzed the lipoprotein patterns in 17 cases and a high incidence of abnormal values was encountered. These data will be the subject of a subsequent report.

Summary and Conclusions

Forty-seven cases of thrombosis of the terminal aorta and iliac arteries have been presented in some detail. The following conclusions have been reached:

1. The syndrome occurs in relatively young persons, predominantly men between 40 and 60 years of age, and is due to localized arteriosclerosis of the terminal aorta and iliac arteries. Signs and symptoms of generalized arteriosclerosis are conspicuously absent.

2. The symptoms consist of intermittent claudication of the hip and hip area which includes the thigh, low back and low abdomen. Forty-six of the 47 cases had this complaint. Frequently, the calf is also involved (20 cases, 42.5 per cent), but always in addition to the hip area. Rarely was impotence encountered (one case only).

3. Examination shows good nutrition in the majority of cases. Thirty-four cases showed good nutrition, eight fair and only five poor nutrition. The pulses are usually absent at all levels. A faint femoral pulsation may be palpable.

4. Aortography is invaluable as a diagnostic aid. It is easily performed and causes little

* See footnote on page 3.

morbidity. It provides information as to the site of the block and the degree of the collateral circulation. In general aortic and common iliac artery occlusions are associated with the most effective collateral circulation. External iliac occlusion is associated with poor collateral blood flow. Three of the five patients with poor nutrition had involvement of the external iliac artery. The most common collateral channels, as seen on the aortogram, are briefly reviewed.

5. Of the 47 cases analyzed 7 had thrombosis of the abdominal aorta, 11 of one common iliac artery, 4 of both common iliac arteries, 2 of one external iliac artery, and 1 of one common iliac artery and the opposite external iliac arteries. One patient had diffuse disease without an occlusion. Three aortograms were unsatisfactory and one was normal. We believe, in contradistinction to Leriche and others, that the disease does not invariably progress from the iliac arteries to involve the aorta, but may remain in the common iliac arteries without progression for many years. The far greater incidence of involvement of the iliac arteries compared with the aorta substantiates this.

6. Conservative treatment with frequent observation is recommended until a practical and satisfactory method of excision and grafting is established. Endarterectomy, resection combined with sympathectomy, or sympathectomy alone are unsatisfactory methods of treatment. Twenty-four patients have been followed on conservative treatment for periods of one to five years and 11 have improved, 10 have remained unchanged and only 3 have become worse. There has been little indication to date that the disease is chronically progressive.

7. We believe the prognosis of the syndrome to be good over a large number of years and we have found no published statistics which prove otherwise.

ADDENDUM

Since this paper was written, we have seen an additional 31 patients with the syndrome; in 21, the diagnosis was proved by aortography. In one of the patients there was progression of the disease from the left common iliac artery into the aorta which was proved by aortography. In one patient with obstruction of the terminal aorta, the disease progressed to a higher level within one month of the time she was first seen at the clinic.

ACKNOWLEDGMENT

We wish to express our thanks to Eugene F. Poutasse, M.D., of the Department of Urology who performed the early aortograms, and to Joseph C. Root, M.D., of the Department of Radiology for his important contribution in the development of the method of aortography which made possible the attainment of consistently excellent films.

SUMARIO ESPAÑOL

Es el propósito de este trabajo el informar el no muy extensamente síntoma clínico de claudicación de la cadera y su relación a oclusión aórtica o de la arteria ilíaca. La importancia de la aortografía en el diagnóstico de este síndrome se enfatiza y la técnica se describe. Los resultados y hallazgos difieren de previos informes en la literatura y las variaciones se discuten.

REFERENCES

[1] GOLDSMITH, G. A., AND BROWN, G. E.: Pain in thrombo-angiitis obliterans: Clinical study of 100 consecutive cases. Am. J. M. Sc. **189:** 819, 1935.

[2] FREEMAN, N. E., AND LEEDS, F. H.: Vein inlay graft in treatment of aneurysms and thrombosis of abdominal aorta, a preliminary communication with report of 3 cases. Angiology **2:** 579, 1951.

[3] OUDOT, J.: La greffe vasculaire dans les thromboses due carrefour aortique. Presse méd. **59:** 234, 1951.

[4] PARSONS, H. G., GERBODE, F., AND COX, A. J.: Studies in aortic autografts and homografts. Do homografts survive? Angiology **3:** 306, 1952.

[5] JULIAN, O. C., DETAKATS, G., AND DYE, W. S.: Segmental nature of peripheral arteriosclerosis: Surgical application. Angiology **4:** 12, 1953.

[6] GROSS, R. E., BILL, A. H., JR., AND PIERCE, E. C., II: Methods for preservation and transplantation of arterial grafts; observations on arterial grafts in dogs; report of transplantation of preserved arterial grafts in 9 human cases. Surg., Gynec. & Obst. **88:** 689, 1949.

[7] —: Coarctation of aorta; surgical treatment of 100 cases. Circulation **1:** 41, 1950.

[8] DOS SANTOS, J. C.: Note sur la désobstruction des anciennes thromboses artérielles. Presse méd. **34:** 544, 1949.

[9] LERICHE, R., AND KUNLIN, J.: Essais de désobstruction des artéres thrombosées suivant la technique de Jean Cid dos Santos. Lyon chir. **42:** 675, 1947.

[10] NÚÑES, A. N., MILANÉS, B., AND IÑIGO, J. R.: Endarterectomy, or surgical restoration of lumen of obstructed artery in arteriosclerosis obliterans. Preliminary report. Circulation **5:** 670, 1952.

[11] FREEMAN, N. E., AND GILFILLAN, R. S.: Regional heparinization after thromboendarterectomy in treatment of obliterative arterial disease, preliminary report based on 12 cases. Surgery **31:** 115, 1952.

[12] LERICHE, R.: De la résection du carrefour aorticoiliaque avec double sympathectomie lombaire pour thrombose artéritique de l'aorte; le syndrome de l'oblitération termino-aortique par artérite. Presse méd. **48:** 601, 1940.

[13] —, AND MOREL, A.: Syndrome of thrombotic obliteration of aortic bifurcation. Ann. Surg. **127:** 193, 1948.

[14] ORTNER, A. B., AND GRISWOLF, R. A.: Chronic occlusion of bifurcation of aorta. Arch. Surg. **61:** 793, 1950.

[15] ELKIN, D. C., AND COOPER, F. W., JR.: Surgical treatment of insidious thrombosis of aorta, report of 10 cases. Ann. Surg. **130:** 417, 1949.

[16] GOODWIN, J. F., AND PETRIE, E.: Insidious thrombosis of abdominal aorta. Brit. Heart J. **13:** 554, 1951.

[17] GREENFIELD, I.: Thrombosis and embolism of abdominal aorta. Ann. Int. Med. **19:** 656, 1943.

[18] BARNETT, W. E., MOORMAN, W. W., AND MERRICK, B. A.: Thrombotic obliteration of abdominal aorta, report of 6 cases. Ann. Int. Med. **37:** 944, 1952.

[19] MILANÉS, B., PEREZ-STABLE, E., AND LASTRA, J. S.: Observations on chronic obstruction of abdominal aorta; Leriche's syndrome. Surgery **28:** 684, 1950.

[20] BOYD, W. M.: Thrombosis of terminal aorta with aortitis and periaortitis, report of 2 cases treated by aortectomy, lumbar sympathectomy, and vena caval ligation. Rocky Mountain M. J. **47:** 936, 1950.

[21] ELLIOTT, R. V., AND PECK, M. E.: Thrombotic occlusion of aorta as demonstrated by translumbar aortograms. J. A. M. A. **148:** 426, 1952.

[22] MCCOMBS, R. P., RHEINLANDER, H. F., COOPER, J. F., AND WALTERS, M. B.: Insidious thrombosis of abdominal aorta with hypercholesteremia. Bull. New England M. Center **12:** 229, 1950.

[23] WELCH, W. H.: Embolism. In Allbutt, C., and Rolleston, H. D., eds.: A System of Medicine, ed. 2. London, Macmillan, 1909. Vol. 6, p. 809.

[24] LUETH, H. C.: Thrombosis of abdominal aorta, report of 4 cases showing variability of symptoms. Ann. Int. Med. **13:** 1167, 1940.

[25] HOLDEN, W. D.: Arteriosclerosis obliterans of abdominal aorta. Arch. Surg. **53:** 546, 1946.

[26] STRAUS, R., DOMINGUEZ, R., AND MERLISS, R.: Slowly progressive occlusive thrombosis of abdominal portion of aorta. Am. J. M. Sc. **211:** 421, 1946.

[27] PRICE, A. H., AND WAGNER, F. B., JR.: Complete occlusion of abdominal aorta; report of 2 patients diagnosed by aortography. Surg., Gynec. & Obst. **84:** 619, 1947.

[28] SPAULDING, W. B.: Thrombotic occlusion of abdominal aorta. Canad. M. A. J. **61:** 162, 1949.

[29] GOODWIN, J. F., AND PETRIE, E.: Insidious thrombosis of abdominal aorta. Brit. Heart J. **13:** 554, 1955.

[30] KEKWICK, A., MCDONALD, L., AND SEMPLE, R.: Obliterative disease of aorta and iliac arteries with intermittent claudication. Quart. J. Med. **21:** 185, 1952.

[31] BOYD, A. M., AND JEPSON, R. P.: External iliac artery thrombosis. Brit. M. J. **1:** 1457, 1950.

[32] LINDBOM, O.: Arteriosclerosis and arterial thrombosis in lower limbs; roentgenological study. Acta radiol. Supp. 80, 1950.

[33] ALLEN, E. V., BARKER, N. W., AND HINES, E. H., JR.: Peripheral Vascular Diseases. Philadelphia, W. B. Saunders, 1946. P. 871.

[34] SHAPIRO, D.: Leriche syndrome (thrombotic obliteration of aortic bifurcation). Am. J. Roentgenol. **67:** 891, 1952.

The Treatment of Tuberculous Pericarditis

By Edwin M. Goyette, Col., MC, USA, Edwin L. Overholt, Maj., MC, USA, and Elliott Rapaport, Capt., MC, AUS

Twenty-seven patients with clinically primary tuberculous pericarditis were treated with prolonged chemotherapy consisting of intermittent doses of streptomycin and daily doses of paraminosalicylic acid or isoniazid. Twenty-one patients did well and were symptom-free six months to three years later. Five, one of whom died, developed constrictive pericarditis. Another died of widely disseminated tuberculosis.

DURING the past four years we have treated 27 cases of clinically primary tuberculous pericarditis. By clinically primary we mean that the signs and symptoms were due to pericarditis and that no other active lesions could be demonstrated clinically at the onset of their illness.

All but two patients were males, the age ranged from 18 to 60. All but five were less than 30 years of age. The age and sex incidence merely reflects the age and sex incidence of our patient population. Sixteen or 59 per cent were Negroes which is significant in view of the fact that Negroes constitute only about 10 per cent of the Armed Forces.

Diagnosis

The etiology was proved in 13 by culture or by demonstrating the organism in tissues removed at operation or autopsy. A presumptive diagnosis was made in four patients by demonstrating a greatly thickened, shaggy pericardium by injecting air into the pericardial sac after the aspiration of fluid. The other 10 patients were diagnosed on clinical grounds, that is, by the presence of a typical, prolonged, severe, febrile illness in a young male, especially a Negro, with a positive Mantoux test, who responds promptly to streptomycin and para-aminosalicylic acid (PAS) or isoniazid (INH), but fails to respond to other therapy and in whom all other causes of pericarditis have been excluded.

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Treatment

Treatment has consisted of bedrest, aspiration for diagnosis and/or relief of tamponade, and chemotherapy. Initially, chemotherapy consisted of streptomycin, 1 Gm. per day. After Deyke[1] showed that intermittent therapy decreased toxicity and delayed the emergence of bacterial resistance, we changed our schedule to 2 Gm. every third day. After it had been shown that para-aminosalicylic acid, added to streptomycin, still further inhibited bacterial resistance and that the two drugs were synergistic,[2] we incorporated the daily administration of 12 Gm. of this substance in our therapeutic regimen. Recently we have substituted isoniazid, 300 mg. daily for the para-aminosalicylic acid. In keeping with the recent trend toward treating minimal tuberculous lesions by prolonged periods of chemotherapy, we have also prolonged the duration of our treatment. Every patient should receive a minimum of 120 days of drug therapy; probably 8 to 12 months is the optimum period. The actual duration of therapy will depend upon the response of the patient, but must be continued for at least 90 days, preferably six months, after all signs of activity have ceased. Our criteria for inactivity are: (1) that the patient is afebrile; (2) that he has a normal sedimentation rate; (3) that there is no evidence of congestion; (4) that he has a normal sized heart with normal pulsations; and (5) that he has a stable, but not necessarily normal, electrocardiogram. After the completion of chemotherapy the patient is slowly, but progressively, ambulated. All of our patients have been hospitalized for at least one year. The duration of treatment has varied

TABLE 1.—*Chemotherapy*

Duration	Streptomycin					PAS				*INH			
	Dose Gm.	q3d	Daily	No.	%	Dose Gm.	Daily	No.	%	Dose	Daily	No.	%
Varying periods	—	—	—	—	—	12	√	8	18.5		√	6	22.2
60 days	1		√	3	11.1	—	—	—	—	—	—	—	—
90 days	1	√	—	3	11.1	10	√	1	3.7	—	—	—	—
120 days	2	√	—	13	63.0	12	√	14	51.8	300 mg.	√	—	—
180 days	2	√	—	3	11.1	12	√	1	3.7	—	—	—	—
210 days	2	√	—	3	11.1	—	—	—	—	—	—	—	—
240 days	2	√	—	2	7.4	—	—	—	—	—	—	—	—
Totals				27	100			24	88.8			6	22.2

* I.N.H. Varied from 30–120 Days.

and is shown in table 1. Several patients received their initial treatment in other hospitals. Two patients have been previously reported.[3]

RESULTS

Chemotherapy was successful in 78 per cent of the entire series and in 69 per cent of the proved cases. Twenty-one patients have done well. They were completely asymptomatic when last seen, and fulfilled all our criteria for an inactive process. The follow-up period has varied from six months to three years after the conclusion of chemotherapy. Six patients were considered treatment failures in that five of them developed constrictive pericarditis. One of these died following surgery, three have undergone successful pericardiectomies, and one refused operation. There was one other death, a young Negro who died of widely disseminated tuberculosis six weeks after the onset of his illness and after only 12 days of chemotherapy.

In analyzing the probable causes of failure, the most constant features were delay in treatment and inadequate dosage. Four of our failures received no chemotherapy until 3 to 11 months after the onset of their disease and all four developed constrictive pericarditis. Another received inadequate therapy in that he received only 1 Gm. of streptomycin twice a week and 10 Gm. of para-aminosalicylic acid daily for only 90 days. At the conclusion of chemotherapy he had already developed constrictive pericarditis. Figure 1 shows graphically the course in one of our patients who underwent prolonged treatment with a good result. Initially he was acutely ill with high fever, elevated venous pressure and a large effusion. Figures 2 and 3 show his chest x-ray films prior to and at the conclusion of chemotherapy. Figure 4 depicts the course in a patient with a poor result where treatment was delayed. His disease progressed and after he had developed constrictive pericarditis he was started on streptomycin and para-aminosalicylic acid. The wide fluctuations in weight were produced by mercurial diuretics, thoracenteses, and paracenteses, the latter indicated by black arrows.

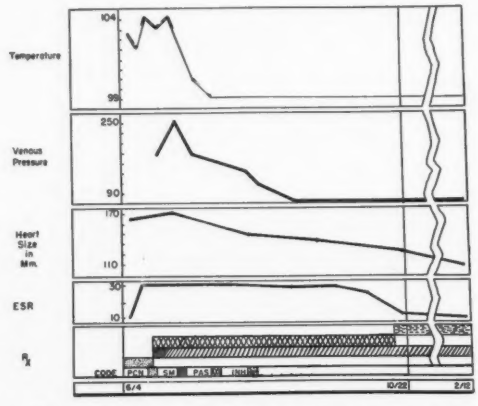
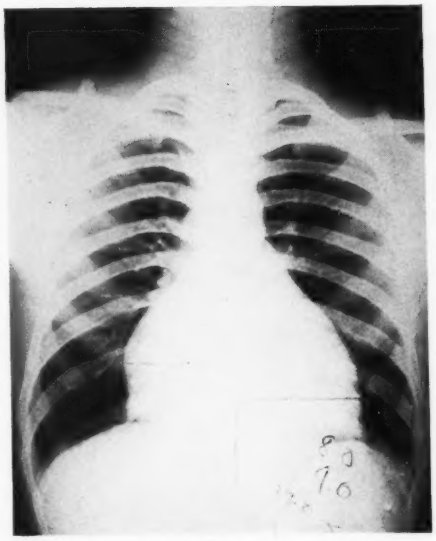


FIG. 1. Condensed graph of a successful case showing temperature, venous pressure, heart size, erythrocytic sedimentation rate and treatment. PCN = penicillin. SM = streptomycin. PAS = para-aminosalicylic acid. INH = isoniazid.



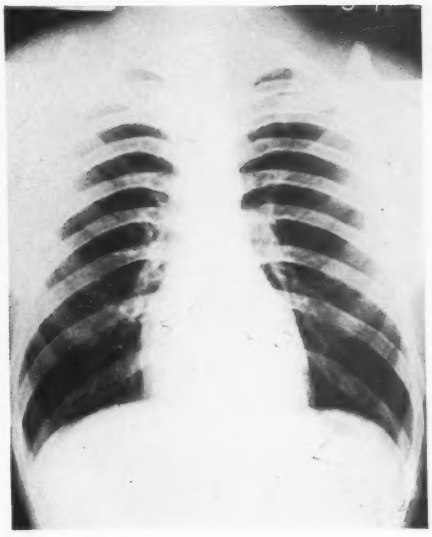


FIG. 2 (*left*). X-ray film of chest showing a large pericardial effusion.
FIG. 3 (*right*). X-ray film of chest of same patient at conclusion of treatment.

He died the day after surgery. Figure 5 is his initial chest film with a massive pericardial effusion and Figure 6 is the chest film taken one month before death, which shows the greatly thickened, shaggy pericardium on contrast radiography

The following factors are those we found most helpful in evaluating the course of their disease: (1) the duration of fever; (2) the duration of the pericardial effusion; (3) the progress of the electrocardiogram and (4) the evolution of congestion. The pertinent points of these factors are shown in tables 2, 3 and 4.

The most important factor in evaluating the result of therapy appeared to be the evolution of congestion. All of our successful cases lost all signs of congestion, but three of our failures had persistent congestion and the other three showed progressive congestion in spite of chemotherapy. Four of our cases have developed full-blown constrictive pericarditis within six months of the onset of their illness and this occurred within three months in two patients. Three had definite constrictive pericarditis when therapy was initiated.

Previous authors have pointed out that the mortality rate is much higher in those cases that are proved bacteriologically.[4, 5] In our series, the overall mortality rate was 8 per cent. Both fatal cases were proved by culture and autopsy. The mortality rate in the proven cases was 15 per cent. This appears to be a significant reduction in the anticipated mortality rate in this disease which is complex and which has a highly variable clinical course.[4, 5] Any evaluation of therapy should await a more prolonged

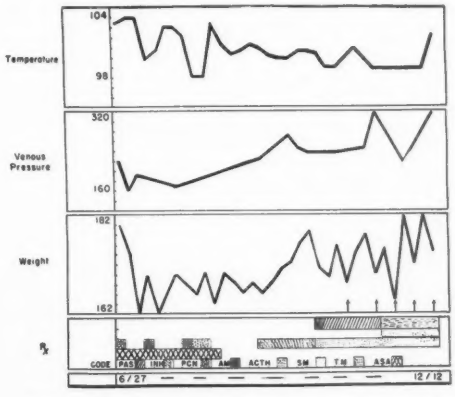
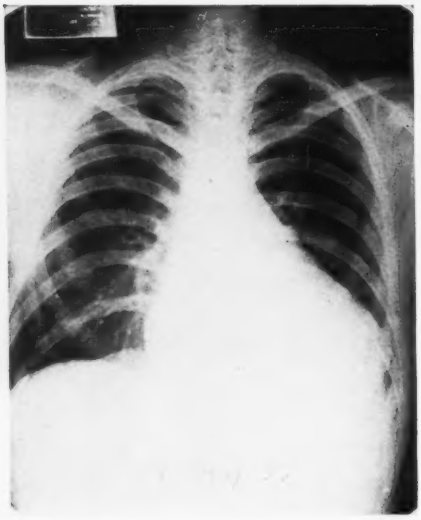


FIG. 4. Condensed graph of an unsuccessful case showing temperature, venous pressure, weight and treatment. Symbols same as in fig. 1. AM = Aureomycin. ACTH = adrenocorticotropic hormone. TM = terramycin. ASA = acetylsalicylic acid.



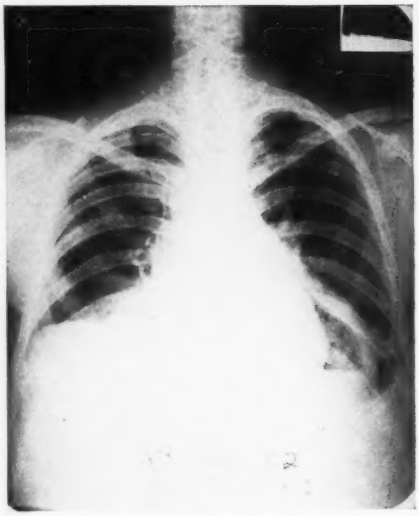


FIG. 5 (*left*). X-ray film of chest of patient shown in figure 4 with a large pericardial effusion.
FIG. 6 (*right*). X-ray film of chest of same patient one month before death. Air has been injected into the pericardial sac.

TABLE 2.—*Duration of Fever*

	Successful	Failure
More than 30 days	3	5
14–30 days	4	1
Less than 14 days	14	0

TABLE 3.—*Duration of Effusion*

	Successful	Failure
Persistent	0	2
6–4 months	3	0
3 months	3	0
2 months	5	2
1 month	9	1
Unknown	0	1
Never definitely present	1	0

TABLE 4.—*Electrocardiogram*

	Successful	Failure
Remained abnormal	5	6
Returned to normal	15	0
Always normal	1	0

follow-up and final conclusions must be deferred until this has been accomplished.

DISCUSSION

Our experience leads us to believe that every case of pericarditis should be studied exhaustively in an attempt to establish the etiology. Diagnostic studies should include pericardial aspiration with culture and/or guinea pig inoculation of the fluid obtained, contrast radiography, and, as a last resort, pericardial biopsy if necessary. We further believe that, when the diagnosis of tuberculous pericarditis is reasonably certain on clinical grounds, treatment should be instituted as soon as the initial studies have been accomplished, and not withheld pending the results of cultural studies or animal inoculations. Six weeks of chemotherapy with intermittent streptomycin and para-aminosalicylic acid or isoniazid is a benign form of treatment. In the event that the diagnosis ultimately proves to be erroneous, no harm has been done and if the diagnosis is later confirmed, valuable time has been gained.

If the patient fails to respond to treatment in spite of adequate medical management, in

that signs of congestion persist or progress, he should be subjected to prompt surgical resection even though active disease is present. It has been conclusively shown that surgical resection can be carried out even in the presence of active disease without danger of dissemination.[6-9] Chemotherapy should be continued throughout the operative period and for at least 90 days, preferably for six months, after attaining an inactive stage.

Summary and Conclusions

1. Twenty-seven patients with clinically primary tuberculous pericarditis were treated with intermittent streptomycin and para-aminosalicylic acid (PAS) or isoniazid (INH).

2. The outcome was considered successful in 21 and unsatisfactory in six patients. Constrictive pericarditis developed in five; one died following surgery, and another of an overwhelming tuberculous infection.

3. The total mortality rate was 8 per cent; in the bacteriologically proven cases it was 15 per cent.

4. Chemotherapy should be initiated early and should include streptomycin, 2 Gm. every third day, and para-aminosalicylic acid, 12 Gm. daily, or isoniazid, 300 mg. daily, and should be continued for at least six months after all signs of activity have ceased.

5. Cases showing persistent or progressive congestion in spite of adequate medical management should be subjected to surgery plus chemotherapy even though active disease is present.

Sumario Español

Veinte y siete pacientes con pericarditis tuberculosa clinicamente primaria fueron tratados con quimioterapia prolongada consistiendo en dosis intermitentes de estreptomicina y dosis diarias de acido paramino-salicílico o isoniazid. Veinte y un pacientes mejoraron y estuvieron libres de síntomas de seis meses a tres años más tarde. Cinco desarrollaron pericarditis constrictiva, uno de los cuales murió. Otro murió con tuberculosis diseminada.

References

[1] Deyke, V. F., Fisher, M. W., James, L. A., and Sides, L. J.: Intermittent dosage schedules of streptomycin with resultant prolonged sensitivity of M. tuberculosis. Ann. Int. Med. **30:** 610, 1949.

[2] Hughes, F. J., Jr., Mardis, R. E., Dye, W. E., and Tempel, C. W.: Combined intermittent regimens in the treatment of non-miliary pulmonary tuberculosis: a comparison of streptomycin every 3rd day and PAS daily with streptomycin every 3rd day and PAS every 3rd day. Dis. Chest **21:** 1, 1952.

[3] Johnson, R. P., and Bercu, B. A.: Streptomycin in the treatment of tuberculous pericarditis. Am. Rev. Tuberc. **5:** 656, 1949.

[4] Blalock, A., and Levy, S. E.: Tuberculous pericarditis. J. Thoracic Surg. **7:** 132, 1937.

[5] Harvey, A. M., and Whitehill, M. R.: Tuberculous pericarditis. Medicine **16:** 45, 1947.

[6] Andrews, G. W. S., Pickering, G. W., and Sellers, T. H.: The etiology of constrictive pericarditis, with special reference to tuberculous pericarditis, together with notes on polyserositis. Quart. J. Med. **17:** 291, 1948.

[7] Falk, A., and Ebert, R. V.: Tuberculous pericarditis treated with streptomycin. J.A.M.A. **145:** 310, 1951.

[8] Holman, E., and Willett, F.: Treatment of active tuberculous pericarditis by pericardiectomy. J.A.M.A. **146:** 1, 1951.

[9] Chamblis, J. R., Jaruszewski, E. J., Brofman, F. L., Martin, J. F., and Feil, H.: Chronic cardiac compression (Chronic constrictive pericarditis). A critical study of sixty-one operated cases with follow-up. Circulation **4:** 816, 1951.

Commissurotomy for Rheumatic Aortic Stenosis

I. Surgery

By C. P. Bailey, M.D., H. E. Bolton, M.D., W. L. Jamison, M.D., and H. T. Nichols, M.D.

As long ago as the middle of 1949 it had been demonstrated by the senior author that any blunt dilating mechanism applied within the stenotic aortic orifice would, upon expansion, force the separation of one or more of the fused commissures. Thus the diminutive valve orifice could be enlarged without the creation of additional insufficiency and with the restoration of such part of the original valve function as the pathologic distortion of the leaflets would permit. In other words the principles and effectiveness of such an aortic commissurotomy would be comparable to those of the similarly named operation for mitral stenosis. It has remained for us finally to develop an instrument and a technic capable of implementing these concepts, and this has at last been accomplished.

THIS IS the first of three articles dealing respectively with (1) the basic concept and methods of performing aortic commissurotomy surgically, (2) comparison of physiologic abnormalities noted preoperatively with the changes produced by aortic surgery, and (3) the selection, medical management, and clinical results obtained by aortic commissurotomy.

Rheumatic involvement of the aortic valve is second in frequency only to mitral valve involvement. In both instances the pathologic developments are parallel and primarily tend to produce stenosis. Early appearance of rheumatic vegetations along the lines of valve closure is followed by fibrosis along the free valve edges and for a variable distance into the adjacent tissue. Commissural fusion begins peripherally (toward the mitral or aortic annulus) and progresses centripetally. This process eventually reduces the mitral orifice to a very small segment of its original semicircular orificial arc, and reduces the aortic orifice to a tiny triangular central passageway (figs. 1 and 2). In either valve the process may be asymmetric leading perhaps to eccentric placement of the mitral opening, or to bicuspid transformation of the aortic valve and orifice (figs. 3 and 4). Subsequent calcific deposition may further deform or distort the valvular elements greatly.

While mitral valve stenosis is considered to be nearly always the end result of rheumatic involvement, many contend that aortic stenosis is usually arteriosclerotic in origin. Others, notably Cabot,[1a] Karsner and Koletsky,[1b] and McGinn and White[1c] feel that aortic stenosis is nearly always of rheumatic origin. The authors would like to present the question of the etiology of aortic stenosis as follows: When aortic stenosis is associated with a known rheumatic mitral valve lesion, as it has been in more than one-half of the cases which we have subjected to aortic surgery, it must be presumed that the aortic lesion is also rheumatic. When a very similar type of aortic lesion (with well marked commissural fusion) is seen without coexisting mitral disease, we believe that it must also be presumed to be of rheumatic origin. On this basis of reasoning we feel that the vast majority of cases of clinical aortic stenosis must be considered rheumatic.

This is not an academic question since the presence or absence of commissural fusion, so characteristic of rheumatic aortic stenosis, is

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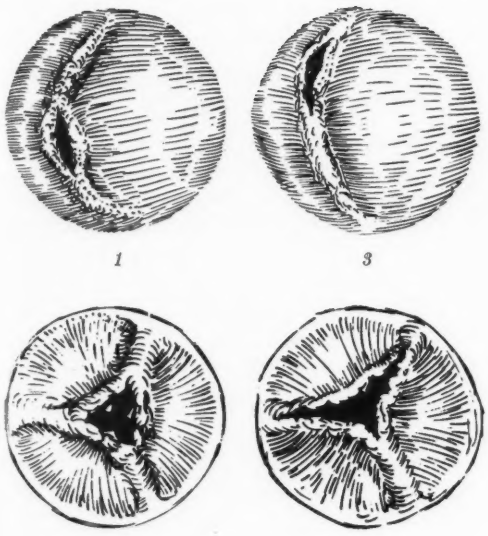


FIG. 1. Gradual fusion of the edges of the cusps of the mitral valve with closure of the anterior and posterior commissures resulting in a stenosed elliptically shaped opening.

FIG. 2. Aortic valve as seen from above with fibrosis and fusion of the commissures resulting in a triangular stenosed orifice.

FIG. 3. Asymmetric mitral valvular stenosis with the opening situated near the anterior commissure with complete fusion of the posterior commissure.

FIG. 4. Asymmetric aortic stenosis as seen from above with almost complete fusion of one commissure resulting in what simulates a bicuspid valve.

the most important single element determining the type and effectiveness of possible corrective valve surgery. The classic congenital case of aortic stenosis is characterized by a funicular or megaphone-like valve structure without evidence of pre-existing commissures (fig. 5). The bicuspid aortic valve is also usually of congenital origin. It may become the site of a superimposed rheumatic stenosis (fig. 6). While such cases certainly present fused commissures and might well be helped by surgical commissurotomy, it would seem that the instrumentation which would here be appropriate would be entirely different from that which has proven effective in the tricommissured valve (fig. 7*a* and *b*).

The arteriosclerotic form of aortic stenosis

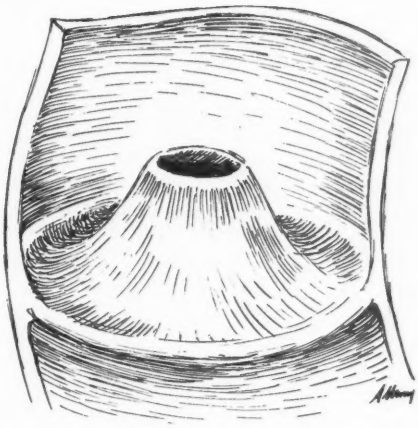


FIG. 5. Congenital aortic stenosis with funicular type of structure and absence of commissures.

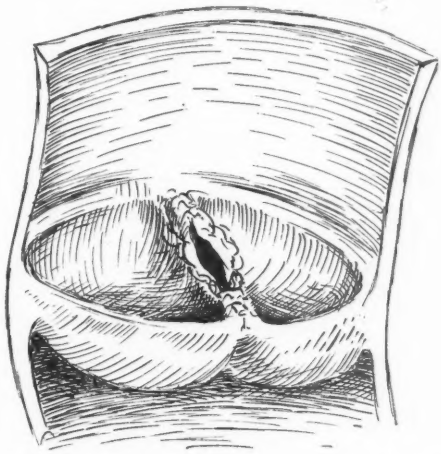
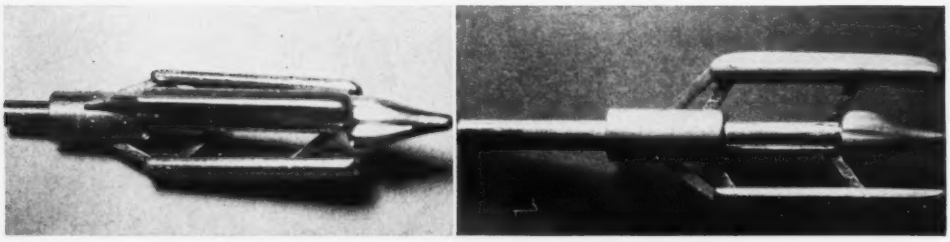


FIG. 6. Congenital bicuspid aortic valve with superimposed rheumatic disease resulting in stenosis.

is characterized by a hardening of the valve leaflets and by deposition of calcium salts. There is characteristically no commissural fusion. In such cases the procedure of commissurotomy would seem to be most inappropriate or even impossible. Indeed any dilating or separating mechanism applied within the lumen of the aortic orifice in such a case will only serve to enlarge the opening momentarily. The semirigid valvular structures tend to spring back into their previous position as soon as the instrument is removed.



a *b*

FIG. 7. (*a*) Triradiate dilator head suitable for rheumatic aortic stenosis involving a previously normal valve. (*b*) Biradiate expanding bars which may be used in the case of a bicuspid aortic valve with superimposed stenosis.

Similarly, subacute (or acute) bacterial endocarditis does not characteristically tend to produce valvular commissural fusion. However, because of its known tendency to become superimposed upon a valve previously damaged by rheumatic disease, one may expect to observe combined cases of rheumatic and bacterial disease. In them, when commissural fusion exists, the possibility of successful application of the principle of commissurotomy also exists, once the active infection has been thoroughly suppressed by antibiotics.

Since its first presentation in June, 1948,[2] the principle of commissurotomy has been successfully applied in cases of mitral stenosis to restore both an adequate valvular orifice and a normal type of valvular function. It still remains the accepted method of correcting this condition surgically. In 1950, commissurotomy was successfully employed in the treatment of rheumatic tricuspid stenosis.[3, 4]

The principle of aortic instrumental commissurotomy has been presented as early as 1950,[5] and an approach through the right common carotid artery (retrograde fashion) has been described. Unfortunately, both that instrument and that approach have since proven faulty. Both have subsequently been greatly modified.

Since the concept of commissurotomy implies a fusion of pre-existing commissures which may be more or less accurately reestablished by separating the valve into its individual anatomic components, its most logical application would seem to be in rheumatic stenotic valvular lesions. While individual cases of congenital, arteriosclerotic, or bacterial aortic stenosis may prove suitable for commissurotomy, the majority will not be amenable to this technic. Mixed cases with both rheumatic and other valvular lesions will, of course, frequently respond favorably to commissural separation.

It must be emphasized that the clinical effectiveness of any commissurotomy technic depends both upon the amount of residual mobility or flexibility which remains in the valvular elements and the valve ring and upon the amount of myocardial vigor and integrity which is retained or can be restored. Both of these considerations suggest that one must not expect great clinical improvement in terminal or near-terminal cases. Our best results can be expected in cases with extensive early commissural fusion, before subsequent extreme distortion and degeneration of the valvular components permanently remove the possibility of return of appreciable valve function. It also seems probable that early mobilization of the fused valve commissures would tend to prevent the development of certain degenerative processes such as extensive calcific deposition upon the fused and immobile valve leaflets.

Efforts to correct aortic stenosis surgically by commissurotomy were maintained during 1950 and 1951. On April 4, 1952, the modern aortic dilator* became available to us. By that time, a reasonably satisfactory transventricular approach to the aortic valve had been de-

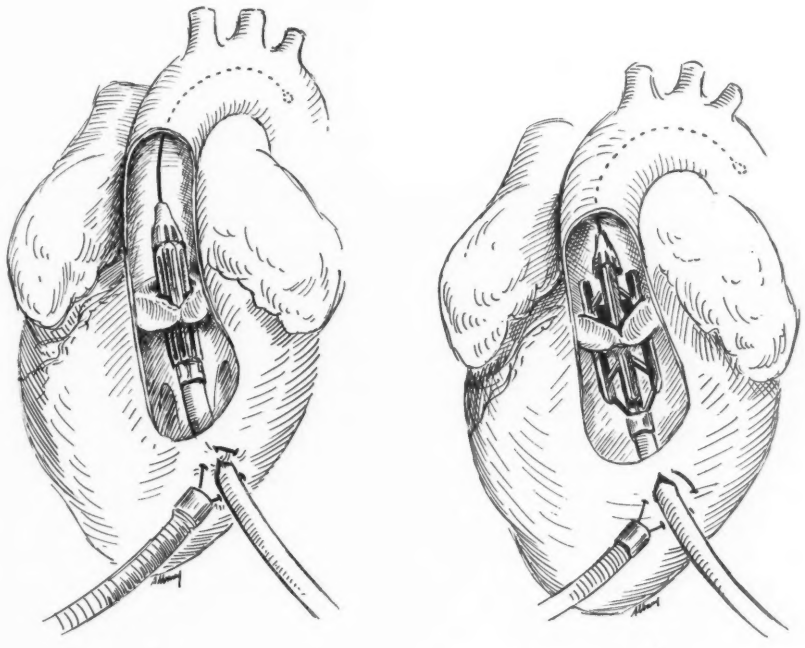
* Manufactured by J. S. Donaldson, Chatham, N. J.; available from G. P. Pilling & Sons, Inc., Philadelphia, Pa.

veloped. The incorporation of the olivary-tipped guide wire or finder (H. P. Larzelere) has proven to be an invaluable addition to the instrument, since it largely obviates the otherwise considerable risk of producing a false passage through the back of the heart. The description of this instrument and our early experience in its employment by the transventricular route have been presented elsewhere.[6-8]

The ability of the triradiate dilating head, which is triangular on cross-section both in the closed and open position, to adjust automatically (by rotation on a swivel mechanism) to the outline of the roughly triangular residual aortic orifice ensures a proper alinement of each wedge-like dilating bar against the appropriate fused commissure. The tendency of the adherent or fused commissures to separate upon expanding pressure is thus exaggerated. Frequently all three commissures will become extensively separated, but at least one or two will invariably part (fig. 8 *a* and *b*).

Thus, a purely instrumental aortic commissurotomy can be accomplished by transventricular passage of the instrument without direct palpation of the valve or accurate visual or digital guidance of the commissurotomy. The immediate surgical results obtained after one year's experience in the use of this instrument by this method are shown in table 1. Physiologic and clinical results obtained will appear in the subsequent papers of this series.

The overall operative mortality in 62 patients operated upon by this technic has been 17.7 per cent, which seems to us to be unduly high even though many of these patients were very ill or even nearly terminal. More than one-half of the cases in this series have been complicated by the coexistence of mitral valve lesions. These associated lesions have been simultaneously subjected to appropriate cor-



a *b*

FIG. 8. (*a*) The dilating head in position in the stenosed aortic valve showing the guide wire extending beyond into the aorta. Purse string at the site of entrance through the left ventricular wall for control of bleeding. (*b*) The dilating head expanded showing the triradiate bars separating the aortic valvular commissures.

TABLE 1.—*Immediate Surgical Results of Commissurotomy with Aortic Dilators, Using Transventricular Approach, in 62 Cases*

Lesion	No. Cases	Early Deaths	Operative Mortality %	Late Deaths	Insuff. Created or Increased
Univalvular (Aortic)					
a) Pure AS	15	3	20.0	0	3*
b) AS & AI	12	3	25.0	0	0
Total	27	6	22.2	0	3*
Multivalvular Lesion					
a) AS & MS	9	1	11.1	1	0
b) AS, AI, MS	7	0	0	0	0
c) AS, AI, MS, MI	13	3	23.0	1	1
d) AS, MI	3	1	33.3	0	0
e) AS, MS, MI	3	0	0	0	0
Total	35	5	14.3	2	1
Grand Total	62	11	17.7	2	4

AI—Not dynamic.

* Two cases were congenital aortic stenosis.

rective surgery, either mitral commissurotomy, 91.4 per cent, or mitral suturing, 8.6 per cent. It is true that this series represents a pioneering or a developmental effort, suggesting that further improvement in selection of patients, in management and in operative technic may lead to significant reduction in mortality.

However, it is disturbing to note that the operative mortality in 27 patients with isolated aortic disease was 22.2 per cent while the mortality of simultaneous combined mitral and aortic surgery in 35 cases was only 14.3 per cent. These seemingly paradoxic results suggest that there may be a singificant difference in the type, or an increase in the severity of the aortic lesion in the univalvular case. One must also consider the possible different physiologic effects of single and multiple valvular lesions and the influence of surgical correction of one lesion upon the other.

The possible differences in the aortic valve lesions might relate to the presence or absence of commissural fusion (etiologic differences), or to the severity of the stenosis. While a patient with both aortic and mitral stenotic lesions may be presumed to have rheumatic commissural fusion of both valves, the patient with only an aortic lesion may not be rheumatic at all. Therefore, the aortic valve may not present commissural fusion and may be completely unsuitable for the surgical technic contemplated. Three of our cases of isolated aortic disease included in this series were considered to be of congenital origin. It is noteworthy that, postoperatively, two of them presented evidence of a created aortic insufficiency. Only two other patients in the entire series of 62, showed a new or increased element of aortic insufficiency postoperatively. It might seem reasonable to presume that when the stenotic lesion of a single valve has brought a patient to his knees, it should be logically a tighter obstruction than that found in either of the two affected valves in a bivalvular case. Hence, one might hypothesize that the very tight univalvular lesion would offer greater surgical technical difficulties and would imply a greater chance of production of ventricular arrhythmias or other disturbances.

More likely, in the specific problem of coexisting aortic and mitral stenosis, the latter lesion prevents ready filling or at least overfilling of the left ventricular chamber and so protects the left ventricle from the worst effects of severe aortic obstruction. Examination of the heart with isolated aortic stenosis reveals the left ventricular wall to be thickened and hypertrophied. There is little or no dilatation of the ventricular chamber. The wall of the hypertrophied left ventricle is frequently very soft and "cheesy" so that properly applied sutures tend to cut through. This undoubtedly represents a form of myocardial degeneration, probably related to the prolonged "isometric" type of contraction necessary to force the ventricular contents through the obstructed aortic orifice. During surgery such a degenerated, hypertrophied ventricle frequently appears to be hyperirritable, manifesting runs of ventricular extrasystoles at the slightest stimulation.

Since there exists a state of relative coronary insufficiency in these cases, because of the existence of the great hypertrophic muscle

TABLE 2.—*Analysis of Cause of the 13 Deaths Occurring in 62 Cases of Aortic Stenosis Subjected to Commissurotomy with Aortic Dilator*

Lesions	Vent. Fib. during operation	Vent. Fib. after operation	Hemorrhage during operation	Hemorrhage after operation	Pulmonary Embolus	Left Vent. Failure	Acute Right Vent. Failure	Increased AI due to Operation
Univalvular								
a) Pure AS	2	1‡						
b) AS & AI	1	1§		1				
Multivalvular								
a) AS & MS			1			1*		
b) AS, AI, MS								
c) AS, AI, MS, MI			1		1		1	1†
d) AS, MI		1¶						
e) AS, AI, MI								
f) AS, MS, MI								

* Late death—4 mos. p.o.
† Late death—4 weeks p.o.
‡ 2 hrs. p.o.
§ ½ hr. p.o.
¶ 13 hrs. p.o.

mass in the presence of a low mean aortic pressure, one may assume that this degenerated, hypoxic myocardium should be particularly predisposed to the development of ventricular fibrillation. The depression of anesthesia and surgery, and the creation of a suitable trigger mechanism by the incising, manipulating, and suturing of the left ventricle would seem an ideal combination to precipitate this usually fatal arrhythmia. Reference to table 2 reveals that of six deaths occurring in the 27 cases of isolated aortic disease, five (83 per cent) were due or presumed to be due to ventricular fibrillation. One other case in this group was successfully defibrillated by massage and electric counter-shock. Manual cardiac "massage" has been found to be most unsatisfactory in these cases because the small left ventricular chamber and the very thick walls make it difficult to expel much blood from the heart manually and hence to produce an adequate output. It is also noteworthy that in one case in this group hemostatic suturing of the incision in the soft left ventricle was extremely unsatisfactory and led to death from ventricular hemorrhage several hours later. Both this ready tendency to irreversible ventricular fibrillation and the uncertainty of adequate hemostasis argue against the use of the transventricular approach to isolated aortic stenotic lesions.

On the other hand, in cases with both aortic and mitral stenosis the left ventricle is usually small, resembling that seen in isolated mitral stenosis. The myocardium of the left ventricle in these cases is characteristically firm and healthy to touch. Sutures hold well, and ventricular extrasystoles are infrequent during their application. These ventricles do not readily fibrillate even during the passage and manipulations of the dilating instrument. If ventricular fibrillation does occur in these cases (as in case F. K.), once both valvular obstructions have been relieved, rhythmic manual compression is very effective in establishing a good cardiac output, and defibrillation by countershock is readily accomplished. It is noteworthy that only one death (6.3 per cent) occurred in 16 patients (table 1) with simultaneoulsy operated combined aortic stenosis and mitral stenosis (with or without associated insignificant aortic insufficiency), the lowest mortality obtained in any group in this operated series. It would seem that the transventricular approach to the aortic valve had, in this group, proved most satisfactory. The thoracic incision here employed (posterolateral approach through the fifth or sixth left intercostal space) fortunately is equally satisfactory for the performance of a simultaneous mitral commissurotomy.

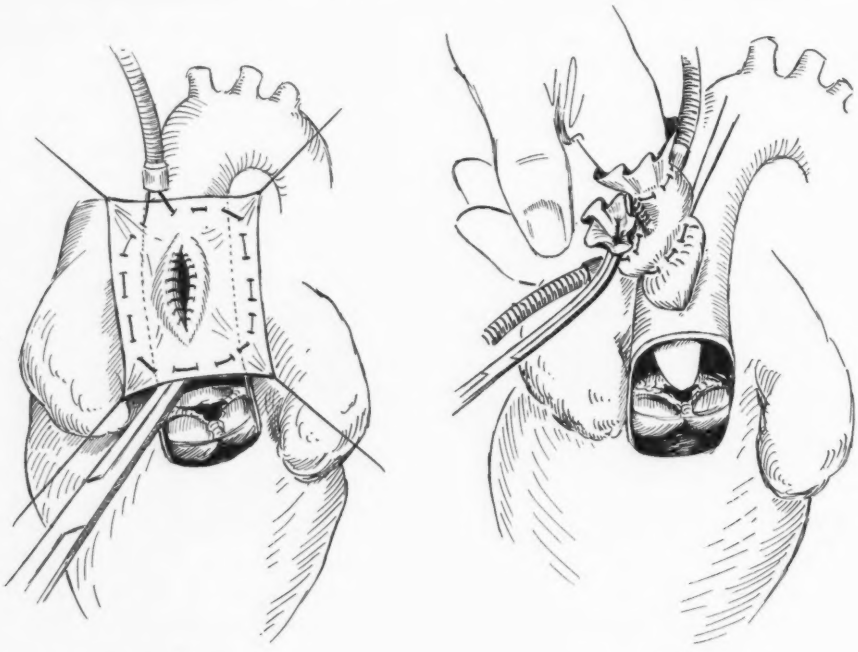
In patients with coexisting aortic stenosis and serious mitral insufficiency the left ventricle is both hypertrophied and dilated. How-

ever, its general muscular firmness and tone seem better than that found in isolated aortic stenosis. In many of these the mitral insufficiency is of great magnitude and is unassociated with mitral stenosis. We believe it is often mainly related to over-stretching or dilatation of the mitral annulus, a result of the enlargement of the left ventricle and the great increase in the intraventricular pressures.

Surgical correction of the incompetent mitral valve by suturing the leaflets with a pericardial strip is, in itself, an operation of great magnitude, which in a series of 80 cases has been associated, in our hands, with a 25 per cent mortality.[9] While this technic was used only in three cases in this series, along with simultaneous aortic commissurotomy, with two deaths, it seems probable that such combined surgery always will be associated inherently with a high operative mortality.

It would seem safer to stage these operations, correcting the aortic stenosis at the first stage. Should the resultant fall in left intraventricular pressure, or subsequent contraction of the mitral annulus lead to improvement in the mitral insufficiency, it might not prove necessary to perform a subsequent mitral suturing operation.

Because of the obvious dangers and difficulties associated with the transventricular approach in certain cases, we have considered other possible approaches to the aortic valve, preferably one permitting digital examination of the valve and tactile guidance of the instrumentation. The Ramirez maneuver,[5] in which the left atrium and mitral orifice are used to approach the left ventricular outflow tract and the aortic valve, has proven in our hands to be extremely dnagerous because of the likelihood of tearing the septal mitral leaflet. Finally, an approach directly through an incision in the ascending portion of the



a *b*

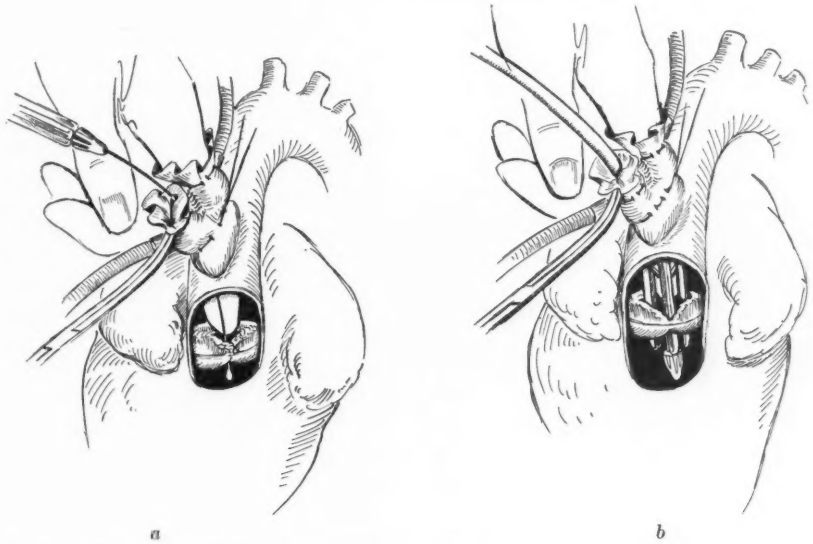
FIG. 9. (*a*) Supravalvular approach to the aortic valve through the ascending aorta. Strip of pericardium sutured to edges of incision into the aorta and purse string applied to periphery of the pericardial strip. A curved Potts clamp is applied for exclusion of this portion of the aorta. (*b*) The left index finger advanced through the "pericardial pouch" for exploration of the diseased valve. A smaller second compartment of the pouch prepared for admission of the aortic dilator.

aortic arch was chosen as a most direct one permitting palpation of the valve cusps and orifice, and facilitating accurate and appropriate instrumentation of the valve.

Accordingly, on March 6, 1953, a patient (R. C.) with both aortic stenosis and insufficiency was operated on through a sternum-splitting incision. A portion of the ascending aortic arch was excluded by a curved Potts clamp. A strip of pericardium, two inches by three inches was sutured to the edges of a longitudinal incision made in the excluded aortic tissue, creating a pouch or "aortic appendage" (fig. 9 *a* and *b*). A purse-string suture of heavy braided silk was placed about its free extremity. The operator's bare left index finger was inserted into the pouch and, as the clamp was released, it was advanced through the aortic incision into the region of the aortic valve. The valve was palpated, commissural fusion was identified, and the valve opening was located and measured. The olivary tip of the guide wire of the aortic dilator was advanced along the intravascular finger tip until it passed accurately through the valve opening into the left ventricle. The operator's finger was then withdrawn as the aortic incision was clamped and the instrument was inserted into the pouch in its place, finally entering the valve orifice in retrograde fashion to accomplish wide dilatation. The aorta was then reclamped and sutured. Subsequently the technic has been modified so that the pouch is divided into two sections allowing insertion of the finger and instrument at the same time (fig. 10 *a* and *b*).

This technic has since been applied with some modification in nine patients. In seven, the sternum-splitting approach was used as described. Then one of us (H. E. B.) suggested the right second intercostal space as less sanguineous and less shocking. This approach has since been utilized twice. Whereas the actual pericardial pouch was used, as described, five more times, it has in two cases been replaced by a rubber-plastic pouch with two finger-like projections. This is sutured to the lips of the aortic incision as described, and then the dilating mechanism of the instrument is entirely enclosed in the longer pouch "finger." The operator's ungloved left index finger is inserted into the other projection (fig. 11).

After removal of the aortic clamp, the finger explores the aortic valve, guides the wire in retrograde fashion through the diminutive



a *b*

FIG. 10. (*a*) The aortic guide wire advanced through the stenotic aortic valve under palpatory guidance with the left index finger. (*b*) The aortic dilator is advanced through the valve orifice and the triradiate bars are expanded to separate the commissures of the valve.

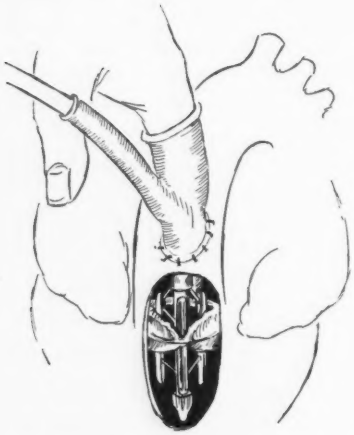


FIG. 11. A rubber-plastic pouch may be used to replace the pericardial pouch.

aortic orifice, feels the dilator head as it becomes engaged in the valve, and subsequently evaluates the effectiveness of the commissurotomy accomplished. The aorta is then reclamped, the pouch is removed, and the vascular incision is closed by one row of everting mattress sutures, and one running suture of fine arterial silk (fig. 12).

The transaortic operation seems to be well tolerated, seems equally effective, and should be safer than the transventricular one because it avoids ventricular injury. However, two early patients died after several days, apparently because of hemorrhagic extravasation from the split sternal edges. It is certain that the right intercostal incision will avoid this complication. In older patients where the aortic wall may be friable, the transventricular approach should be preferable.

While our present experience has obviously been meager with this transaortic technic, it has already been possible to make certain important observations. For instance, we were amazed to find that the actual remaining valve orifice in two cases was so small as to barely admit the olivary tip of the guide wire (3 to 4 mm. diameter). It is almost unbelievable that life can be maintained with such a severe degree of aortic obstruction. Undoubtedly attempts must be made to treat these patients at an earlier stage.

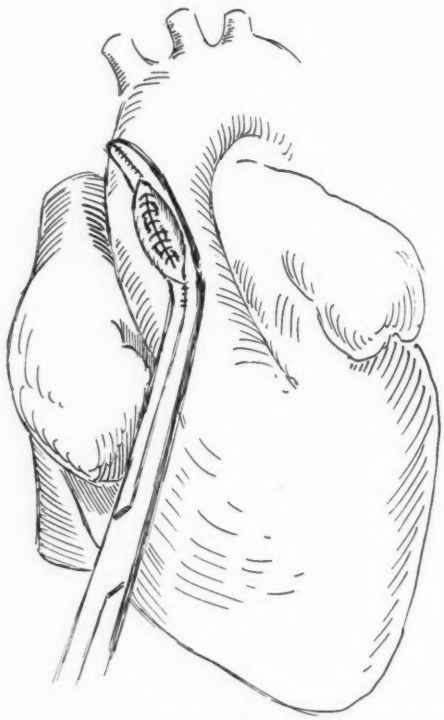


FIG. 12. The curved Potts clamp applied to the aorta, the pouch removed, and the incision closed.

Again, we were surprised that the amount of surgically produced valvular enlargement was somewhat less than we had expected, even when the dilator head was opened to the fullest extent. While our present dilator head is apparently adequate for aortic commissurotomy in average-sized females, it is evident that a larger head is necessary for maximal improvement in large males. A larger sized dilator head is now in process of manufacture.

The presence or absence of calcification, the presence or absence of commissural fusion, and some idea of the amount of coexisting aortic regurgitation can be readily established by transaortic digital palpation.

SUMMARY

The rheumatic stenotic aortic valve may be approached for surgical commissurotomy either by the transventricular or the transaortic route.

We feel that many young patients with iso-

lated aortic stenotic disease should be operated upon from above.

Probably patients with aortic stenosis and mitral insufficiency should be operated upon from above at the first operative stage. The mitral lesions should be sutured at a subsequent operation from below, if this operation is still considered necessary.

We feel that cases of combined aortic and mitral valve stenosis should continue to be operated upon at one stage from below. The simplicity of the necessary surgery and the low combined operative mortality experienced in this type of patient seem to justify this belief.

We feel that commissurotomy for rheumatic aortic stenosis is a sound, logical, and extremely effective operation. With individualization of the operative approach in the different types of cases, and with greater experience in selection and management, we feel that it bids fair to rank with mitral commissurotomy in safety and in clinical effectiveness.

Sumario Español

Desde mediados del año 1949 se ha demostrado por el autor "senior" que cualquier mecanismo de dilatación obtusa aplicado dentro del orificio aórtico estenótico, al expandirse separaría una o más de las comisuras fundidas. De esta manera el orificio diminutivo valvular puede ser agrandado sin la creación de una insuficiencia adicional y con la restauración de parte de la función original de la valvula permisible por la distorción patológica de los pliegues. En otras palabras, los principios y la efectividad de una comisurotomía aórtica serían comparables a aquellos de la operación para estenosis mitral. A descansado en nosotros el desarrollar un instrumento y una técnica capaz de llevar a cabo estos conceptos y esto ha sido finalmente logrado.

REFERENCES

[1a] Cabot, R. C.: Facts on the Heart. Philadelphia, Saunders, 1926.

[b] Karsner, H. T., and Koletsky, S.: Calcific Disease of the Aortic Valve. Philadelphia, Lippincott, 1947.

[c] McGinn, S., and White, P. D.: Clinical observations on aortic stenosis. Am. J. M. Sc. **188:** 1, 1934.

[2] Bailey, C. P.: The surgical treatment of mitral stenosis (mitral commissurotomy). Dis. Chest **15:** 377, 1949.

[3] —, Glover, R. P., and O'Neill, T. J. E.: The Surgery of valvular heart disease. Dis. Chest **20:** 5, 453, 1951.

[4] —, — and —: Transmyocardial palpatory surgery of the heart. Canad. M. A. J., **66:** 529, 1952.

[5] —, —, —, and Redondo-Ramirez, H. P.: Experiences with the experimental surgical relief of aortic stenosis: preliminary report. J. Thoracic Surg., **20:** 516, 1950.

[6] —, Redondo-Ramirez, H. P., and Larzelere, H. P.: Surgical treatment of aortic stenosis. J.A.M.A. **150:** 1647, 1952.

[7] Larzelere, H. B., and Bailey, C. P.: New instrument for cardiac valvular commissurotomy. J. Thoracic Surg. **25:** 1, 78, 1953.

[8] —, and —: Aortic commissurotomy. J. Thoracic Surg. **26:** 31, 1953.

[9] Bailey, C. P., Bolton, H. E. and Redondo-Ramirez, H. P.: Surgery of the mitral valve. Surg. Clin. North America, **32:** 1807, 1952.

Cation Uptake by Exchange Resin in Vitro and the Colon as a Sodium-Conserving Organ

By Henry Field, Jr., M.D., Leon Swell, Ph.D., D. F. Flick, M.S., and Robert E. Dailey, M.S.

Cation-exchange resins have not fulfilled early expectations. Those in clinical use do not retain much sodium in the feces when dietary sodium is much restricted. Comparison of the sodium and potassium bound by a resin, in equilibrium with presumably normal electrolytes as found in the terminal ileum, with the amounts of those ions in the feces, permits an over-all evaluation of two major factors operating in the gastrointestinal tract. These are a decreased sodium concentration in the terminal ileal contents when sodium intake is restricted and an absorptive power of the colon sufficient to detach sodium from the resin.

It has been a consistent observation that cation-exchange resins will retain much more sodium in the feces of experimental animals or patients who are consuming diets with a liberal sodium content than when dietary sodium is much restricted. When subjects have been maintained on diets with unrestricted sodium intake, a carboxylic cation-exchange resin similar to the one used in this study has been found to retain in the feces 0.5 to 2.5 mEq. of sodium and 0.4 to 2.9 mEq. of potassium per gram of resin.[1] When diets containing between 500 and 800 mg. of sodium per day were consumed the resin has bound, in the feces, 0.26 to 0.80 mEq. of sodium and 0.27 to 2.32 mEq. of potassium per gram of resin.[2]

The reason for these differences in the amount of sodium fixed by the resin in the feces when subjects are taking liberal and low sodium diets has been obscure. There is, normally, a large amount of sodium in the secretions of the gastrointestinal tract, to which the resin is exposed. It has been suggested that "endogenous" sodium does not combine with cation-exchange resin in the intestinal tract and that the sodium removed in the feces by the resin is "exogenous" sodium of dietary origin.[3]

It is difficult to understand why the resin should react differently with sodium of different origins. It has seemed necessary to seek a better explanation for the seemingly different behavior of the resin to "exogenous" and "endogenous" sodium. The uptake of cations by exchange resins depends upon the following factors[4]: (a) concentration of ions, (b) pH of the medium, (c) the relative affinity of the resin for different cations and (d) the concentration of resin.

In the gut, there are other possible mechanisms that might effect the uptake of sodium by exchange resins. One is the previously unexplored possibility that the sodium concentration of the contents of the ileum may become decreased when the sodium content of the diet is much restricted. McCance[5] reported a decreased sodium content of gastric juice, saliva and sweat in subjects who were maintained on low sodium diets. Studies which are in progress, utilizing dogs with ileal fistulas, indicate that the concentration of sodium in the terminal ileum is considerably decreased during sodium deprivation.

There is also the possibility of absorption of sodium by the colon, against the gradient of the affinity of the resin for it. Whether there is an active absorption of ions from the gut or whether their absorption is by a simple process of diffusion has long been a subject of controversy. In most of the large volume of experimentation concerning intestinal absorption, loops of the small bowel have been used. The intestinal contents normally reach the terminal ileum with their electrolytes approximately in equilibrium with those of the plasma,[6, 7] al-

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though a rather wide range of values has been reported by Lockwood and Randall.[8] In contrast, there is relatively little sodium in the feces. In agreement with that, the preponderance of evidence from direct experiments with loops of colon, reported by Goldschmidt and Dayton[9] and Visscher and his associates,[10, 11, 12] is indicative of active absorption, against osmosis, by the colon. Among others, Odel and Ferris[13] have successfully used a solution in approximate electrolyte equilibrium with the plasma for dialyzing lavage of the small intestine in the treatment of renal insufficiency. However, when they used the same solution for dialyzing lavage of the colon,[14] of 40.5 liters of solution run in through an appendicostomy tube in 64 hours, only 24.5 liters were recovered through the rectal tube and their patient became edematous. There has been, thus, abundant evidence of active absorption of electrolytes by the human colon. It remains to be determined if the power of the human colon to absorb electrolytes is sufficient to affect the retention of sodium in the colon by cation-exchange resins.

There has also been evidence that absorption of electrolytes is subject to hormonal influence. Dennis and Visscher[15] found that excitement was associated with a decreased rate of absorption from loops of the ileum in the trained unanesthetized dog. Anesthetization of excited dogs increased the rate of absorption, while anesthetization of placid dogs caused no such change. Dennis and Wood[16] found that adrenalectomized dogs, maintained on high sodium, high bicarbonate and low potassium diets, had a marked decrease in the rates of absorption of sodium, potassium and chloride from the ileum. This was reversed in each instance following the administration of adrenal cortical extract. When the cortical extract was withdrawn, the rate of sodium absorption in general declined more than that of potassium. At times there seemed to be an actual reversal in the direction of movement of sodium with excretion of it into the intestinal tract in relatively large amounts, although potassium was still being absorbed. Leaf and Couter[17] found indirect evidence of changes in adrenocortical activity, in normal human subjects, associated with changes in the salt content of their diets. Berger, Quinn and Homer[18] reported that desoxycorticosterone acetate (DOCA) decreased the fecal excretion of sodium in rats and also in human subjects. In another study, Berger and Steele[19] reported that less sodium was retained in the feces of edematous cardiac and cirrhotic patients, by cation-exchange resin, than in control subjects.

In this study, the sodium and potassium fixed by a carboxylic cation-exchange resin* exposed, in vitro, to a solution containing approximately the electrolyte concentrations of the contents of the terminal ileum, as reported by Lockwood and Randall,[8] have been determined and compared with the amounts of those ions per gram of resin present in the feces of patients.

Methods and Materials

In vivo experiments. Five male patients were used in these studies. The patients were compensated cardiacs on low sodium diets and were receiving no diuretic medication other than digitalis. The diets were prepared under the direction of the hospital dietitian and contained 0.8 to 1.2 Gm. of sodium per day. The diets were restricted in potassium to the extent of omitting fruit juices and salt substitutes. Forty-five Gm. of carboxylic cation-exchange resin in the ammonium and potassium form (ratio of one part potassium to two of ammonium) were fed daily to each patient except patient Ly who received the hydrogen cycle form of the resin, as will be explained. The resin was given in three 15 Gm. doses in water daily following meals.

Feces were collected daily in cardboard containers, using carmine dye as a marker, pooled for analysis, and mixed by an electric mixer into three-day specimens. Twenty-four hour urine samples were collected daily and blood samples were taken every three days for determinations of their sodium and potassium contents.

The feces samples were weighed out in crucibles, four-normal sulfuric acid added and the samples heated on a hot plate to dryness. The residue was ashed in a muffle furnace at 550 C. overnight. The ash was dissolved in hydrochloric acid and analyzed for sodium and potassium content. The sodium and potassium determinations were carried out on the Barclay flame photometer with an internal lithium standard. The sodium and potassium con-

* Resodec and its equivalent in the hydrogen cycle form were kindly supplied by the Smith, Kline and French Company.

tents of urine and serum were determined directly after appropriate dilution.

In vitro experiments. A mixture of sodium chloride, sodium hydroxide and potassium chloride which had approximately the average ionic concentration of the contents of the terminal ileum as reported by Lockwood and Randall,[8] was equilibrated with known amounts of cation-exchange resin in the hydrogen-cycle form. The solution had the following composition: 129.4 mEq. per liter of sodium as sodium chloride and sodium hydroxide, 11.2 mEq. per liter of potassium as potassium chloride and 116.2 mEq. per liter of chloride as potassium chloride and sodium chloride. The solution was made up in Aminosol (protein hydrolysate) to give a final concentration of 2.5 per cent of the hydrolysate.

The resin was weighed out, mixed with 1000 cc. of the solution, and shaken for one hour on a shaking machine. The pH of the solution was determined before exposure to the resin and then after shaking. The mixture was filtered and the resin was dried overnight at 100 C. The resin was analyzed for sodium and potassium after ashing. Experiments were conducted in which the supernatant, washed and unwashed resin were analyzed. Analysis of the supernatant introduced considerable error due to the large dilution while direct analysis of the washed or unwashed resin gave consistent results; there was no significant loss of sodium or potassium when the resin was washed.

Results and Discussion

In Vitro. It will be seen in table 1 that only 1 or 2 Gm. of the carboxylic resin, in the hydrogen cycle, could be equilibrated with 1 liter of the solution without lowering its pH below the physiologic range encountered in the terminal ileum. As the solution became increasingly more acid with increasingly large amounts of the resin, there was a progressive decrease in the total uptake of cations per gram of resin. However, the findings of Karr and Abbott[6] concerning the contents of the ileum, obtained by a Miller-Abbott tube after feeding of hydrochloric acid, indicate that the hydrogen-ions released from the resin, when it is taken therapeutically, would be absorbed in passage. Consequently, it would appear that, with the proportionately larger amounts of resin used in the in vivo experiments, the final equilibrium in the terminal ileum would have been at the normal pH. Thus, the uptake of cations per gram of resin, in the terminal ileum during the intestinal passage in patients would be expected to be that found in these experiments at the final pH values of 7.1 and 6.8. That was 2.79 and 2.34 mEq. of sodium, respectively, and 0.18 mEq. of potassium per gram of resin. (This does not allow for the probability that the concentration of sodium in the terminal ileum may be decreased during sodium depletion.) The sodium to potassium ratio under these conditions was 7:1.

Table 1.—*The Uptake of Cations by Exchange Resin from a Solution Containing the Approximate Ionic Concentration of Enterostomy Fluid**

Amt. Resin Gm./L.	Initial pH	Final pH	Cation Uptake	
			Na mEq./Gm. resin	K mEq./Gm. resin
1	7.5	7.1	2.79	0.18
2	7.5	6.8	2.34	0.18
4	7.5	6.3	1.52	0.12
8	7.5	5.7	0.88	0.08
10	7.5	5.5	0.70	0.08

* The solution, before equilibration, contained the concentrations: Sodium, 129.4 mEq./L.; potassium, 11.2 mEq./L. and chloride, 116.2 mEq./L., which were the average values for those ions in the contents of recent ileostomies, as reported by Lockwood and Randall.[8]

In Vivo. The sodium and potassium contents per gram of resin in the feces of five patients, representing 211 patient-days of resin administration, was quite different from the uptake of cations under the conditions existing in the terminal ileum as indicated by the in vitro experiments. This is shown in table 2 and in table 3. In the latter table the average fecal sodium for the entire group, over that period of time, is contrasted with the uptake by the resin when in equilibrium in a solution with the

Table 2.—*The Urinary and Fecal Excretion and Serum Cation Levels in Patients Receiving Cation-Exchange Resin**

Patient	Days on Resin	Serum		Urine		Feces		Feces	
		Na mEq./L.	K mEq./L.	Na mEq./day	K mEq./day	Na mEq./day	K mEq./day	Na mEq./Gm. Resin	K mEq./Gm. Resin
Du.	48	140	3.9	13.9	46.2	18.3	31.8	0.41	0.71
St.	48	143	4.2	46.1	64.1	25.7	35.9	0.57	0.80
Sto.	48	146	4.2	0.6	12.8	28.3	112.6	0.63	2.50
Te.	43	150	4.2	39.1	67.0	17.4	41.3	0.39	0.92
Ly.	24	135	3.9	32.2	66.7	6.1	79.2	0.13	1.76

* All figures represent average values.

approximate electrolyte composition of the contents of the terminal ileum.

There was a considerable difference between different patients in the sodium content of their feces and, consequently, in the proportion of total sodium excretion which was renal. Ninety-seven and nine-tenths per cent of patient Sto's sodium excretion, neglecting sodium in sweat, was by his feces and he averaged only 0.6 mEq. of sodium per 24 hours in his urine. In contrast, patient Ly had only 15.9 per cent of his sodium excretion in his feces. It is possible that that difference in the amount of sodium retained in the feces by the resin in these patients was related to hormonal activity such as has been demonstrated in the experiments referred to.[15-19] Patient Ly had malignant hypertension. He had been severely decompensated a few weeks before this experiment and he died a few weeks after its completion. Patient Sto was a normotensive with arteriosclerotic heart disease who for one and one-half years had been maintained in cardiac compensation only with the assistance of the resin or of mercurial diuretics.

Even patient Sto, who had the highest proportion of his sodium excretion by his feces, had only 0.63 mEq. of sodium per gram of resin in his feces. This is in contrast with the 2.5 mEq. of sodium per gram of resin which is the approximate amount which would have been bound by the resin when in equilibrium with the presumed contents of the terminal ileum during consumption of a normal diet.

It is to be noted that the colon does not absorb potassium as actively as it does sodium. In fact, the absorptive power of the colon for potassium is so weak that the cation-exchange resin, by its affinity for potassium, was able to withdraw from the colon average amounts, per patient, of potassium ranging from 28.2 mEq. in 24 hours for patient Te to 92.3 mEq. per 24 hours for patient Sto. Those are the average amounts of fecal potassium of those patients after deducting the 12.8 mEq. of potassium per 24 hours that is normally present in feces[20] and the 8.1 mEq. of potassium that would have been bound by 45 Gm. of the resin in the terminal ileum, as indicated by the results of the in vitro experiments. In those experiments, it was found that the carboxylic cation-exchange resin bound only 0.18 mEq. of potassium under the conditions usually found in the terminal ileum. In contrast, the patients had each an average amount of potassium in their feces ranging from 0.71 to 2.50 mEq. (average for all periods of all patients, 1.52 mEq.) per gram of resin. The average ratio of sodium to potassium in all feces was 0.3:1, which contrasts with the ratio of 7:1, in the in vitro experiments.

TABLE 3.—*A Comparison of the Cation Uptake by Exchange Resin in Vitro and in Patients on a Low Sodium Diet*

	Na *mEq./Gm. Resin*	K *mEq./Gm. Resin*	Total *mEq./Gm. Resin*
In vitro*	2.34	0.18	2.52
In vivo†	0.48	1.52	2.00

* The resin was exposed to a solution containing the approximate composition of the contents of the terminal ileum; final pH, 6.8.

† These figures represent the average daily fecal excretion of five patients for 211 patient-days during administration of the resin.

Despite that large withdrawal of potassium in the feces, all of the patients had moderate to large amounts of potassium in their urines, as is indicated in table 2. Nevertheless, with the moderate restriction of potassium intake resulting from the omission of fruit juices and salt substitutes, all of the patients except Ly, who had potassium supplements throughout, suffered potassium depletion. The other four patients had declines in their serum potassium concentrations to 3.0 to 3.2 mEq. per liter before they were given potassium supplements. The figures for serum potassium given in table 2 are average values. Presumably, the patients would have experienced muscular weakness if their activity had not been limited. Tarail and Elkington,[21] among others, have observed the continued urinary excretion of potassium by patients despite their having already suffered potassium deficiency. The withdrawal of potassium in the feces by exchange resins has been a concern to all investigators. Neither the colon nor the kidney are effective conservers of potassium.

Patient Ly had marked renal insufficiency with nitrogen retention. The resin, as it is marketed, would have been contraindicated because of its ammonia content and its acidifying potentiality. He tolerated the resin very well, in the hydrogen cycle, while its acidifying effect was neutralized by appropriate doses of potassium citrate.

There is to be considered the possibility of a decreased sodium concentration in the terminal ileum, due to the restriction of dietary sodium, which is inferred because of the finding by McCance[5] of decreased concentrations of sodium in the saliva, gastric juice and sweat of patients subjected to a similar restriction of dietary sodium. However, assuming that its pH remained normal, the sodium concentration of the contents of the terminal ileum would have had to be reduced to 26.0 mEq. per liter for the resin, in equilibrium with it, to have bound only the 0.63 mEq. of sodium per gram of resin which was found in the feces of patient Sto. It would have had to have been reduced to 22.5 mEq. per liter (about one-sixth of the normal concentration[8]) for the resin to have bound the 0.48 mEq. of sodium per gram of resin, which represents the average fecal sodium of all five patients, for 211 patient-days.

In our opening discussion, we have referred to the previous evidence that the colon is capable of active absorption of sodium against a concentration gradient, and that that absorption is subject to hormonal influence. The above data (table 3), comparing the amounts of sodium bound by this carboxylic resin when it is in equilibrium with electrolytes, as they have been found to occur in the contents of the terminal ileum,[8] with the amount of sodium, per gram of resin, found in the feces is further evidence of the power of the colon to absorb sodium against a gradient. It can overcome the affinity of the resin for sodium sufficiently so that, in most patients, it detaches from the resin and absorbs a major portion of the sodium which should have been bound to the resin as it passed the terminal ileum.

Active absorption of sodium by the colon, together with the probable decreased sodium concentration in the terminal ileum of patients with a restricted dietary sodium, greatly impairs the ability of this carboxylic cation-exchange resin to augment the sodium depletion which is possible by dietary restriction alone. Perhaps, in many circumstances, that is fortunate. There have been several reports of the low salt syndrome in patients on low sodium diets, although dietary effects were usually augmented with mercurial diuretics.[22, 23, 24] Patient Sto, with a rather moderate restriction of dietary sodium and customary doses of this resin, maintained a normal serum sodium, but only by a narrow margin. For many weeks his urinary sodium excretion averaged 12 mg. per 24 hours. A cation-exchange resin with a greater affinity for sodium at the pH existing in the colon would have been advantageous in the treatment of the other four patients. It would have been disastrous to patient Sto, without the advantage of laboratory control or the timely clinical recognition of the low salt syndrome.

A further concept is supported by these data. It would appear that the colon has a role in the conservation of sodium almost comparable, in many patients, with that of the kidney. From previously reported evidence[15-19] this sodium conserving function of the colon appears to be subject to hormonal influence. Among our patients there was a wide variation in the absorptive ability of the colon to detach sodium from its bonds to the resin or, possibly, in the decreased concentration of sodium in their ileums. Experiments are in progress, using dogs with fistulas into their terminal ileums, to obtain direct information concerning the absorption of sodium from their colons during the feeding of the resin.

Summary and Conclusions

A carboxylic cation-exchange resin has been equilibrated in vitro with a solution so constituted that its electrolyte content approximated that which has been found in the contents of the terminal ileum. The resin in that equilibrium fixed much more sodium and much less potassium than was found, per gram of resin, in the feces of five patients over prolonged periods.

It appears that the colon has sufficient power to absorb sodium so as to overbalance the affinity of the resin for sodium. The colon has a role in the conservation of sodium which may be, in many patients, almost comparable to that of the kidney. The colon gives up large

amounts of potassium to the resin. Neither the colon nor the kidneys are effective conservers of potassium.

Sumario Español

Resinas de intercambio de cationes no han producido los resultados esperados. Aquellas en uso clínico no retienen mucho sodio cuando el sodio en la dieta se restringe mucho. Comparación del sodio y el potasio atado a la resina, en equilibrio presumiblemente con los electrólitos normalmente hallados en el íleon terminal, con las cantidades de estos iones en las heces, permite una evaluación generalizada de los dos factores mayores operando en el tracto gastrointestinal. Estos son, una diminucion en la concentracion del sodio del contenido del íleon terminal cuando hay restricción en la ingestión del sodio y el poder de absorción del colon suficiente para separar sodio de la resina.

REFERENCES

[1] Greenman, L., Peters, J. H., Mateer, F. M., Weigard, F. A., Wilkins, D., Tarail, R., Rhodes, G., and Danowski, T. S.: Biochemical changes accompanying the ingestion of a carboxylic cation exchanger in the hydrogen, ammonium, sodium, potassium, or calcium form. J. Clin. Investigation **30:** 995, 1951.

[2] Emerson, K., Jr., Kahn, S. S., Vester, J. W., and Nelson, K. D.: Oral use of cation-exchange resins in treatment of edema. Arch. Int. Med. **88:** 605, 1951.

[3] Bonner, C. D.: Electrolyte-balance studies in normal volunteers and clinical observations on the effects of cation-exchange resins in patients with cardio-vascular disease and in subjects receiving pituitary adrenocorticotrophic hormone (ACTH), New England J. Med. **247:** 158, 1952.

[4] Ch'en, J. S., and Freeman, S.: The removal of cations from solutions and the rat's alimentary canal by H-form resins. J. Lab. & Clin. Med. **35:** 99, 1950.

[5] McCance, R. A.: The effect of salt deficiency in man on the volume of the extracellular fluids and on the composition of sweat, saliva, gastric juice and cerebro-spinal fluid J. Physiol. **92:** 208, 1938.

[6] Karr, W. G., and Abbott, W. O.: Intubation studies of the human small intestine. IV. Chemical characteristics of the intestinal contents in the fasting state and as influenced by the administration of acids, of alkalies and of water. J. Clin. Investigation **14:** 893, 1935

[7] Welch, C. S., Wakefield, E. G., and Adams, M.: Function of the large intestine of man in absorption and excretion. Arch. Int. Med. **58:** 1095, 1936.

[8] Lockwood, T. S., and Randall, H. T.: The place of electrolyte studies in surgical patients. Bull. N. Y. Acad. Med. **25:** 228, 1949.

[9] Goldschmidt, S., and Dayton, A. B.: Studies in the mechanism of absorption from the intestine. I, II, III, IV and V. Am. J. Physiol. **48:** 419, 433, 440, 450 and 459, 1919.

[10] Burns, H. S., and Visscher, M. B.: Influence of various anions of lyotropic series upon sodium and chloride content of fluid in intestine. Am. J. Physiol. **110:** 490, 1944.

[11] Ingraham, R. C., and Visscher, M. B.: Further studies on intestinal absorption with the performance of osmotic work. Am. J. Physiol. **121:** 771, 1938.

[12] Visscher, M. B., Varco, R H., Carr, C. W., Dean, R. B., and Erickson, O.: Sodium ion movements between the intestinal lumen and the blood. Am. J. Physiol. **141:** 488, 1944.

[13] Odel, H. M., and Ferris, D. O.: Continuous lavage of the small intestine as a means of treating renal insufficiency: Report of a case. Proc. Staff Meet., Mayo Clin. **23:** 201, 1948.

[14] —, and —: Continuous lavage of the colon as a means of treating renal insufficiency: Report of a case. Proc. Staff Meet , Mayo Clin. **23:** 209, 1948.

[15] Dennis, C., and Visscher, M. B.: The influence of various factors upon intestinal absorption involving osmotic work in the unanesthetized dog. Am. J. Physiol. **129:** 176, 1940.

[16] — and Wood, E. H.: Intestinal absorption in the adrenalectomized dog. Am. J. Physiol. **129:** 182, 1940.

[17] Leaf, A., and Couter, W. T.: Evidence that sodium excretion by normal human subjects is regulated by adrenal cortical activity. J. Clin. Investigation **28:** 1067, 1949.

[18] Berger, E. Y., Quinn, G. P., and Homer, M. A.: Effect of desoxycorticosterone on the colon: Its relation to the action of cation exchange resins in man. Proc. Soc. Exper. Biol. & Med. **76:** 601, 1951.

[19] —, and Steele, J. M.: Suppression of sodium excretion by the colon in congestive heart failure and cirrhosis of the liver demonstrated by the use of cation exchange resins. J. Clin. Investigation **31:** 451, 1952.

[20] Wiley, F. H., and Wiley, L. L.: Inorganic salt balance during dehydration and recovery. J. Biol. Chem. **101:** 83, 1933.

[21] Tarail, R., and Elkington, J. R.: Potassium deficiency and the role of the kidney in its production. J. Clin. Investigation **28:** 99, 1949.

[22] MacGuire, W. B., Jr.: Risk of uremia due to sodium depletion. J.A.M.A. **137:** 1377, 1948.

[23] Soloff, L. A., and Zatuchni, J.: Syndrome of salt depletion. J.A.M.A. **139:** 1136, 1949.

[24] Schroeder, H. A.: Renal failure associated with low extracellular sodium chloride. J.A.M.A. **141:** 117, 1949.

Norepinephrine in Shock Following Myocardial Infarction

Influence upon Survival Rate and Renal Function

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A clinical study is presented of the influence of continuous intravenous norepinephrine therapy upon shock accompanying myocardial infarction. The significant reduction in immediate and eventual mortality rates usually associated with this condition are discussed. Complications are defined, and a possible first reported instance is presented of ventricular tachycardia developing in the presence of complete heart block during the administration of large doses of norepinephrine.

SEVERE and sustained hypotension complicating myocardial infarction is correlated with a fatality rate[1] between 80 per cent and 90 per cent. It may be assumed that hypotension and the accompanying inadequate coronary circulation are detrimental to the functional integrity of the myocardium and therefore warrant prompt correction. The various therapeutic measures employed until recently have not provided relief of marked sustained hypotension, nor have they substantially influenced the high fatality rate. This report presents an evaluation of the influence of continuous norepinephrine therapy upon immediate and eventual survival from shock occurring in patients with myocardial infarction.

METHODS AND MATERIALS

Criteria for Therapy. The plan for treating patients in shock was to administer phenylephrine hydrochloride (Neo-Synephrine) or other pressor amines by the intramuscular or intravenous route intermittently as indicated. If the systolic blood pressure was elevated to above 100 mm. Hg and satisfactorily maintained, further therapy was withheld. On recurrence of shock similar medication was employed through one to three episodes. Norepinephrine by continuous drip was instituted if (1) the patient was known to have been in shock longer than one hour, (2) the initial episode of shock was severe with systolic pressure below 80 mm. Hg for at least 15 minutes, (3) more than three transient episodes of shock had occurred within 12 hours, (4) or if Neo-Synephrine proved ineffective in relieving any episode of shock.

Pharmacology. l-Norepinephrine has the following pharmacologic effects:

1. Constriction of peripheral arteries, capillaries and veins,[2] an effect which is probably not mediated through neural pathways or via the adrenal cortical hormones.
2. Slowing of the heart rate when the vagi are intact and increasing the rate when the vagi are blocked.[3]
3. Increasing the coronary artery blood flow, resulting in elevation of oxygen content of coronary sinus blood and of infarcted myocardium.[4]
4. No significant change in cardiac output.[5]
5. Decreasing cerebral blood flow.[6]
6. Induction of ectopic ventricular arrhythmias in complete heart block and other conditions which are largely experimental.[7]
7. Alteration of renal function:[8]
   a. Depression of sodium and potassium excretion.
   b. Constriction of efferent renal arterioles with resultant reduction of the total renal blood flow but increased glomerular filtration fraction.
   c. Increased urine formation.

The pharmacologic actions most likely to cause concern in the prolonged use of this drug, especially in high concentration, were increased cardiac work precipitating heart failure, gross impairment of renal function, and induction of ventricular fibrillation or tachycardia. One possible example of the latter was observed in this series.

Administration. Norepinephrine was administered intravenously after diluting 4 mg. of the bitartrate monohydrate (Levophed*) in 1000 ml. of 5 per cent aqueous solution of dextrose. The use of solutions containing sodium chloride was avoided because of

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* Levophed supplied through the courtesy of Winthrop-Stearns, Inc . New York, N. Y.

the renal retention of sodium in patients with myocardial infarction.[9] The flask was connected to one arm of an "Y" tube, the other arm being clamped off. A pressure clamp controlled the rate of flow which was observed in the filter chamber. When prolonged administration was necessary a polyethylene tube was threaded into the vein in place of a needle. Care was used to avoid and limit extravasation of the solution into the subcutaneous tissues.

The flow was started at approximately 10 drops or 2.5 micrograms of norepinephrine per minute. Blood pressures were determined at intervals of 30 to 60 seconds initially, and after each change in rate of flow until the response was apparent and stabilized. Rise of the blood pressure was often abrupt and pronounced necessitating immediate readjustment of the flow.

The rate of administration was regulated to maintain the systolic blood pressure at about 100 mm. Hg which was usually adequate to abolish the manifestations of shock. In previously hypertensive patients a systolic pressure of 110 to 125 mm. Hg was sought. When therapy was prolonged, the output of an adequate volume of urine was an added criterion of appropriate response.

If the pressor response was inadequate or could be maintained only with a rate of flow exceeding 40 drops per minute, a higher concentration of norepinephrine was administered from a second flask connected to the other arm of the "Y" tube. Concentrations varying from 2 to 32 mg. per liter and doses of 1.5 to 150 micrograms per minute were used depending upon the necessities of maintaining the blood pressure, avoiding excessive fluid intake and preventing clot formation in the needle or catheter resulting from very slow rate of flow.

Blood pressures and flow rates were determined every 15 minutes for at least three hours and every 30 minutes for the remaining period of this therapy. When discontinuance of the drug was contemplated, and after trial on a lowered dosage, an infusion of 5 per cent dextrose solution was maintained for several hours to permit rapid resumption of the pressor therapy if shock returned. Although norepinephrine deteriorates rapidly in an alkaline medium, Ringer's solution and citrated blood were occasionally administered simultaneously through the "Y" tube from the accompanying flask without loss of the pressor effect.

Records were kept of the concentration of the drug, rate of flow in drops per minute, blood pressure, pulse rate and rhythm, fluid intake and urine output, and untoward responses. Renal function studies included the measurement of water balance and, in some cases, determination of renal blood flow by para-aminohippuric acid clearances and glomerular filtration rate by means of endogenous creatinine clearance tests.

Results

Prolonged intravenous norepinephrine therapy was given to 30 patients, ages 43 to 84 (table 1). All had clinical and electrocardiographic evidence of recent myocardial infarction, 19 with involvement of the anterior wall and 11 with involvement of the posterior wall. There were 19 males and 11 females. Five of the patients were previously hypertensive. Infarction occurred in three cases during or shortly after major surgical operations. In one patient shock followed the intravenous administration of procaine amide for ventricular tachycardia.

Fourteen patients experienced recurrent episodes of hypotension with transient recovery in three following intravenous blood transfusions and in eight following Neo-Synephrine injections. Sixteen had been in persistent shock for longer than one hour or were in very severe shock. All patients treated exhibited systolic blood pressures of 80 mm. Hg or below except for four previously hypertensive individuals who manifested shock with systolic blood pressures between 88 and 100 mm. Hg.

Initial therapy consisted of 500 ml. intravenous blood transfusions in five cases, three with transient benefit and two without apparent effect. All five of these responded subsequently to norepinephrine. Intermittent doses of Neo-Synephrine in 16 cases provided transient elevation of the blood pressure in all but four. Three of the latter and all of the former responded to sustained norepinephrine infusions.

Twenty (67 per cent) of the 30 patients survived the episode of shock under norepinephrine therapy, and 16 (53 per cent) recovered clinically and were later discharged from the hospital. Four patients died subsequent to successful treatment of the shock, one from cardiac rupture eight hours later, two others abruptly 4 and 18 days later, and one from Stokes-Adams attacks (ventricular fibrillation) 19 days later. Ten patients (33 per cent) died during norepinephrine therapy (table 2). Seven of these manifested pressor responses, and the other three exhibited hypo-

TABLE 1.—*Clinical Data in 30 Patients Treated with Norepinephrine*

Case	Age, Sex	Location of Infarct	Shock			Prior Therapy
			After Infarct	Duration	Intermittent or Sustained	
1 M. M.	61-M	Anterior	36 hrs.	5½ hrs.	Int.	Neo-Syn. X 3
2 G. F.	78-F	Postlateral	8 hrs.	3½ hrs.	Int.	Neo-Syn. X 2
3 W. L.	66-M	Anterolat.	5 hrs.	40 min.	Sus.	Blood I–V
4 B. A.	65-M	Posterior	29 hrs.	15 min.	Sus.	—
5 E. L.	73-F	Anterior	?	15 min.	Sus.	Neo-Syn. X 1
6 H. T.	72-M	Anteroseptal	7 hrs.	30 min.	Sus.	Neo-Syn. X 1
7 B. S.	44-F	Anterolat.	22 hrs.	15 min.	Sus.	—
8 R. S.	55-M	Posterior	41 hrs.	1 hr.	Int.	—
9 A. W.	55-M	Postlateral	68 hrs.	14 hrs.	Int.	Neo-Syn. X 4
10 K. M.	64-M	Anterolat.	?	25 hrs.	Sus.	Epineph. X 30
11 A. A.	72-M	Anteroseptal	72 hrs.	3½ hrs.	Int.	Blood I–V
12 S. R.	83-M	Anterolat.	?	20 min.	Int.	Blood I–V
13 M. C.	67-M	Anterolat.	45 min.	40 min.	Int.	Blood I–V
14 H. F.	65-F	Anteroseptal	78 hrs.	15 min.	Sus.	—
15 T. L.	57-M	Anterior	18 hrs.	45 min.	Sus.	Neo-Syn. X 2
16 G. B.	63-F	Posterior	7 hrs.	20 min.	Int.	Neo-Syn. X 1
17 J. H.	78-M	Anterior	5 days	4 hrs.	Int.	Neo-Syn. X 5
18 S. S.	70-F	Anteroseptal	4 days	45 min.	Sus.	—
19 R. B.	64-M	Anterior	10 hrs.	11 hrs.	Int.	Neo-Syn. X 4
20 R. G.	55-F	Posterior	4 days	30 min.	Int.	Neo-Syn. X 1
21 S. K.	51-M	Posterior	36 hrs.	1 hr.	Sus.	Neo-Syn X 2
22 I. S.	46-M	Anteroseptal	6 days	14 hrs	Int	Neo-Syn X 8
23 E. B.	82-F	Postlateral	1 day	4½ hrs.	Sus.	Neo-Syn. X 6
24 R. W.	70-F	Anterolat.	3 days	1½ hrs.	Int.	—
25 E. G.	43-M	Anterior	14 days	1 hr.	Sus.	Neo-Syn. X 2
26 I. B.	71-M	Anterior	1 hr.	3 hrs.	Sus.	Blood I–V
27 C. L.	67-F	Posterior	4 hrs.	30 min.	Sus.	Neo-Syn. X 2
28 M. W.	70-F	Posterior	?	6 hrs.	Sus.	Neo-Syn. X 3
29 F. F.	84-M	Anterior	?	5 hrs.	Sus.	Neo-Syn. X 5
30 M. G.	72-M	Posterior	7 days	1½ hrs.	Int.	—

tension resistant to doses as high as 60 micrograms per minute.

Certain observations of the norepinephrine therapy are summarized in table 3.

1. With one exception the duration of shock prior to treatment was over twice as great in the patients who died as in those who survived.

2. Seven of the 10 patients who died during therapy did so within six hours of the start of treatment. The exceptions were one who relapsed into shock when the flow stopped after 70 hours of successful therapy and failed to respond to reinstituted treatment, a second who died abruptly after 181 hours of continuous therapy, and a third who died of ventricular fibrillation. The survivors required from three hours to five and one-half days of continuous treatment.

3. The average dose needed to elevate the blood pressure initially was more than two times as great in those that died as in the survivors.

4. The average maximum dose needed in attempts to maintain the blood pressure in the fatal cases was over five times as large as in the survivors.

Examples of some characteristic findings are demonstrated by the following five cases.

Case 8 (fig. 1) illustrates the transient effect of Neo-Synephrine and the prompt response to 3 to 4 micrograms per minute of norepinephrine. The pressure fell rapidly when the flow was obstructed, but responded promptly again when therapy was restored. In general a stable level of blood pressure was maintained by minor adjustments in dosage to correct the tendency of the pressure to fluctuate. The blood pressure was sustained at a safe level without norepinephrine after a two-hour trial of very low dosage. The pressure did not rise with a con-

TABLE 1.—*Continued*

Case	Maximum Dose/min. *Microgram*	Duration Therapy *Hours*	Total Dose *mg.*	Results*	Remarks
1	11	28½	13	A	None
2	14	69	22	A	Onset infarct during surgery
3	16	40	19	A	Onset postoperatively
4	9	46	18	A	Phlebitis
5	15	69	36	A	Phlebitis
6	5	11½	4	A	Small dosage
7	8	3½	1.6	A	None
8	4	66½	12	A	None
9	5	136	26	A	Phlebitis
10	10	119	64	A	Phlebitis
11	6	94½	16	A	Onset postoperatively
12	5	15	4	A	Phlebitis
13	24	87	67	A	Skin slough
14	15	49	39	A	Cortisone potentiation
15	8	7	4	A	None
16	12	15½	10	A	Phlebitis
17	6	30	7	B	Died 18 days later
18	6	34	10	B	Died 19 days later
19	4	16	4	B	Died 4 days later
20	12	4	4	B	Cardiac rupture 8 hrs. later
21	150	181	420	C	Ventricular tachycardia
22	20	1	0.8	C	None
23	5	1½	0.5	C	Recurrent Stokes-Adams
24	12	6	4	C	Abrupt death
25	25	11½	12	C	Procaine amide caused shock
26	32	70	92	C	Died when flow ceased
27	16	5	4	C	B.P. 120/118 with therapy
28	24	1½	8	D	No pressor effect
29	60	5	8	D	No pressor effect
30	35	4½	7	D	No pressor effect

* A = Survived shock, clinical recovery; B = Survived shock, died later of other causes; C = Died during therapy despite pressor response; D = Died during therapy, no pressor response.

stant dose to indicate that the drug was no longer required.

Case 9 (fig. 2) demonstrates the pattern of a patient who had been in shock intermittently for 14 hours with four significant but transient pressor responses to Neo-Synephrine. The instability of the natural mechanisms controlling blood pressure necessitated continual readjustment of dosage through five and one-half days of therapy. This case represents the unusual example in which a rising pressure is observed on a fixed or decreasing dose indicating that need for the drug was diminishing. In the majority of the patients, continued need for the drug could only be determined by cautiously lowering the dose and observing whether the blood pressure fell.

Case 25 (fig. 3) illustrates the requirement of a large dose (25 micrograms per minute) to maintain a satisfactory and stable blood pressure level. The initial episode of shock followed the intravenous administration of 200 mg. procaine amide for ventricular tachycardia and did not respond to Neo-Synephrine. To prevent recurrence of the paroxysmal ventricular tachycardia, a slow infusion of the procaine amide was then maintained. In spite of this therapy a second episode of the arrhythmia developed, and a precipitous fall in pressure followed the supplementary injection of 250 mg. procaine amide. Both times the blood pressure rose from undetectable levels to satisfactory levels with the use of norepinephrine. Death was due to abrupt ventricular tachycardia and fibrillation. In view of the occurrence of the initial episode prior to therapy, this instance of arrhythmia should not properly be attributed to norepinephrine toxicity.

Case 14 (fig. 4) illustrates extreme instability and wide fluctuation of the blood pressure despite a constant and moderately large dose. The possible stabilizing effect of 150 mg. cortisone orally is demonstrated as is the reduction in dose of norepinephrine required. Cessation of pressor therapy resulted in gradual return of shock but reinstituted therapy re-

TABLE 2.—*Results of Norepinephrine Therapy*

Norepinephrine in Myocardial Infarction—30 Cases	
Survival of Shock—20 (67%)	
Clinical Recovery—16 (53%)	Subsequent Death—4 (13%)
Death During Therapy—10 (33%)	
Pressor Effect—7 (23%)	No Pressor Effect—3 (10%)

stored the pressure appropriately. In previous experiences with cortisone alone, doses of 300 mg. daily were ineffective in correcting hypotension following myocardial infarction. However, in one patient who had been refractory to Neo-Synephrine, a pressor response to this drug was exhibited four hours after receiving 150 mg. cortisone orally. It has been shown experimentally that cortisone sensitizes the contractile elements of the blood vessels to the pressor drugs,[10] and potentiates their effect.[11]

Case 21. This patient required exceptionally large doses of norepinephrine to sustain the blood pressure. The electrocardiogram demonstrated the pattern of a posterior myocardial infarction and complete A-V block with a ventricular rate of 48. The complete heart block persisted throughout the patient's illness. During the fourth day of continuous norepinephrine therapy ventricular tachycardia supervened while the drug was being administered at the unusually high but necessary rate of 150 micrograms per minute. Quinidine controlled the paroxysm which did not return despite similar high doses of norepinephrine during the succeeding three days. This represents the only instance in our series of a ventricular arrhythmia which might be attributed to norepinephrine toxicity, though such have been demonstrated in the experimental animal.[12]

Renal Function

Urine Volume. In no instance did urine volume exceed 20 ml. per hour during the observed period of shock. Of the patients that responded to norepinephrine, only one exhibited oliguria (21 ml. per hour) during the therapy. The remainder showed adequate urine output, averaging 70 to 110 ml. per hour. There was generally a 20 per cent to 50 per cent positive water balance.

Although oliguria, possibly under hormonal influence,[9] is a common complication of myocardial infarction, our patients showed a striking improvement in urine output during norepinephrine therapy, presumably due to elevation of effective filtration pressure. Under

TABLE 3.—*Comparative Observations in Surviving and Fatal Cases*

Norepinephrine in Myocardial Infarction		
	Survival of Shock—20	Died during Therapy—10
Prior Duration of Shock	½–25 Hrs. (Ave. 1.8)	½–15 Hrs. (Ave. 4.0)
Duration of Therapy	3–136 Hrs. (Ave. 59.5)	1½–181 Hrs. (Ave. 29.2)
Initial Effective Dose	2½–20 μg./Min. (Ave. 7)	3–50 μg./Min. (Ave. 18.2)
Max. Dose Needed	1½–24 μg./Min. (Ave. 7.4)	4–150 μg./Min. (Ave. 39.8)

similar conditions of hydration, the urine flow in three cases during norepinephrine therapy and several days afterward was approximately identical, namely 1.64 and 1.78 ml. per minute, 1.42 and 1.25 ml. per minute, and 4.1 and 4.4 ml. per minute, respectively.

Clearances. The para-aminohippuric acid clearances were lower during norepinephrine therapy than subsequent to the infusions despite similar levels of blood pressure and urine minute volumes. In three patients the renal plasma flow measured by this test rose from 120.5 to 157 ml. per minute (31 per cent), from 300 to 384 ml. per minute (28 per cent), and from 355 to 509 ml. per minute (42 per cent), respectively, after stopping the therapy. Glomerular filtration rates were approximately the same during and after therapy, namely 30 and 36 ml. per minute, 68 and 63 ml. per minute, and 54 and 58 ml. per minute. This conforms with previous observations[13] that while renal plasma flow is reduced, glomerular filtration rate is essentially unchanged. A higher filtration fraction results from the apparent efferent arteriolar constriction. No clinical evidence of renal functional defects were observed nor was azotemia present even after five and one-half days of continuous norepinephrine therapy in another patient. The low creatinine clearances in all three of the above patients suggests that primary renal disease, probably nephrosclerosis, existed.

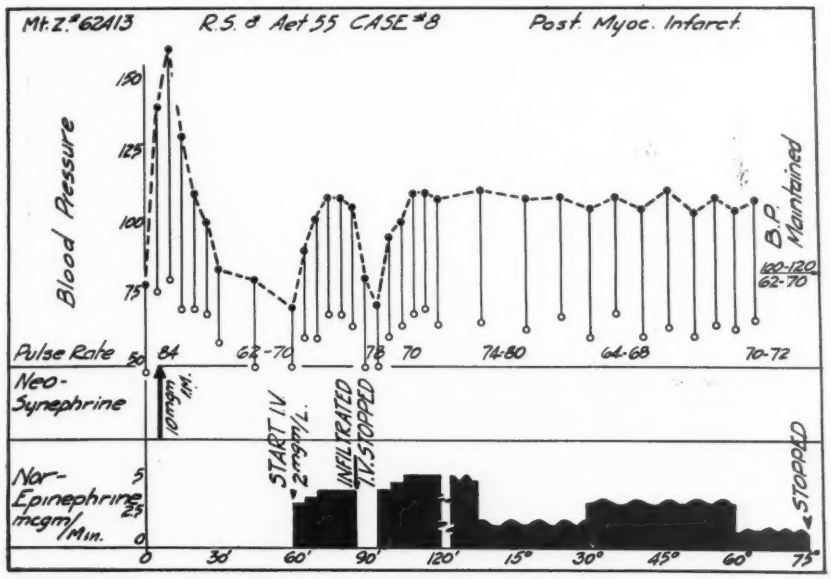

FIG. 1. Case 8. Therapy and blood pressure

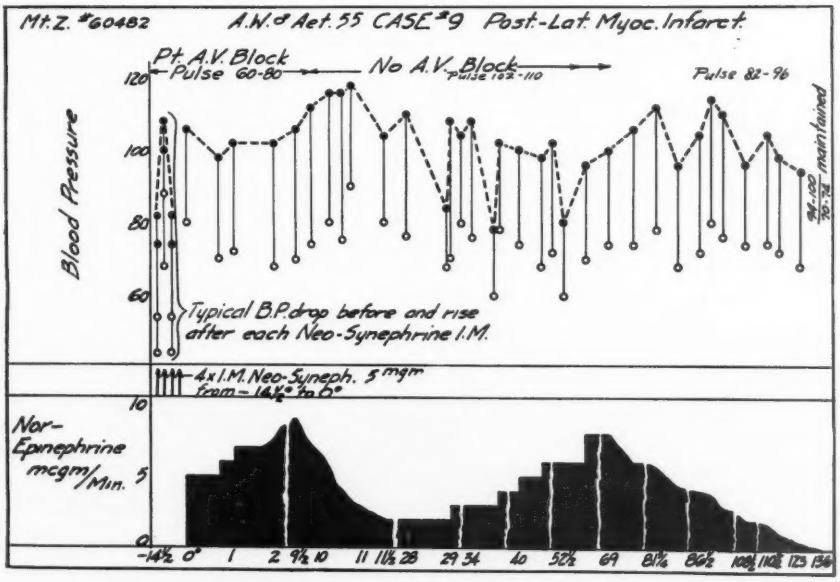

FIG. 2. Case 9. Therapy and blood pressure

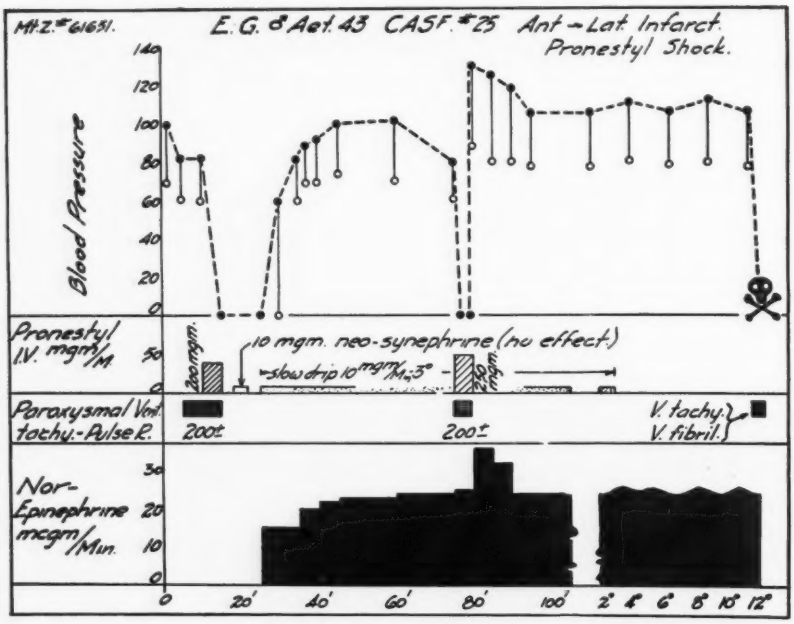

FIG. 3. Case 25. Therapy and blood pressure

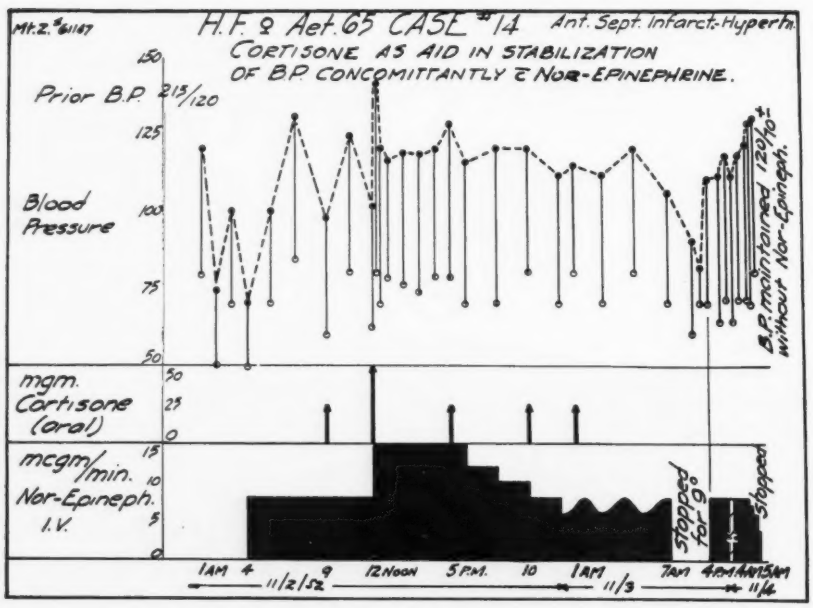

FIG. 4. Case 14. Therapy and blood pressure

Complications

Congestive heart failure was not observed to increase in any of our cases during the therapy. Two instances of arrhythmia were recorded. Norepinephrine probably bore no causal relationship to one (case 25) as noted above. In the other patient (case 21) high doses of norepinephrine may be incriminated in the precipitation of ventricular tachycardia in the presence of complete heart block. Six patients developed mild phlebitis localized above the site of venous infusion. One patient had a large slough of skin and subcutaneous tissue where the solution leaked around a polyethylene tube in a vein of the lower leg. A skin graft was necessary in this case.

Discussion

The mechanism of the shock-like state complicating myocardial infarction has not been completely explained. There are probably both cardiac and peripheral vascular components involved.[14, 15, 16] Systolic ballooning of the ventricular myocardium seems to be related to the shock and is corrected by its relief.[17] Hypotension may follow immediately after the onset of the infarct, in which case about 50 per cent of the patients recover spontaneously within one hour, or it may be delayed for several hours to several days. The delayed gradual onset of shock following myocardial infarction has been described[14] as the clinical manifestation of progressive failure of the infarcted left ventricle and as almost invariably fatal. In our series, 16 of the 20 patients who recovered from episodes of shock with norepinephrine therapy developed the severe hypotension five hours or more after the infarction, and nine of these were delayed for more than 24 hours.

The division of patients with shock into two categories, those with low venous pressure and those with elevated venous pressure,[16] for purposes of different therapy is not borne out in this study. The former was attributed to peripheral vascular or neurogenic reflex mechanisms and was treated with pressor agents, whereas the latter was presumed to reflect profound heart failure and was treated by rapid digitalization, pressor agents being deemed contraindicated here. In our series, several patients in shock with elevated venous pressures responded satisfactorily to norepinephrine pressor therapy alone.

The necessity for promptly correcting this shock state is becoming increasingly apparent, but it is difficult to evaluate the effect of therapy upon immediate and eventual recovery, because patients may exhibit early spontaneous improvement. Withholding specific treatment may permit the exhibition of this spontaneous response. However, if hypotension is severe, such delay may result in irreparable damage to other poorly irrigated areas of myocardium or in "irreversible" shock. It is apparent, therefore, that severe shock should be treated promptly.

The therapeutic measures employed until the past two years included rapid intravenous or intra-arterial infusions of blood or plasma, and individual or intermittent doses of pressor amines: ephedrine, Paredrine, Propadrine, desoxyephedrine, Neo-Synephrine and Mephentermine. Mephentermine, in addition, has been employed in a continuous slow intravenous drip for one-half to one and one-half hours.[1] None of these measures appeared to induce arrhythmias or aggravate congestive heart failure. However, their influences were necessarily transient, and their chief value was in bridging the critical period of one or more episodes of severe hypotension.

In personal experiences with intravenous and intra-arterial infusions of blood and plasma,[18] beneficial results rarely occurred if shock had existed for longer than four hours. In other series[19] a significant percentage of favorable responses are reported to most forms of routine therapy for such cases of shock, provided treatment was instituted within three hours. Thus in shock accompanying myocardial infarction, as in surgical or hemorrhagic shock, an apparently irreversible state often develops after several hours. However, in spite of the frequency of this observation, such irreversibility after prolonged shock is not a constant finding. Patients in this series who had been in shock for three or more hours were often resistant even to con-

tinuous norepinephrine therapy. However, of those who responded and recovered, nearly 40 per cent had been in shock longer than three hours, and one for 25 hours before coming under our care. The mechanisms resulting in "irreversible" shock may be self correcting if sufficient time is given for recovery. Such recovery may be quite abrupt after days of virtually artificial maintenance of blood pressure.

Persistent shock could not be attacked effectively with previous methods of intermittent therapy. The introduction of norepinephrine in a sustained intravenous drip by Kappert[20] presented a more rational means of treating shock from various causes. Subsequent studies[21, 22, 23] demonstrated effective application of such therapy to shock accompanying myocardial infarction. Other pressor amines may prove equally satisfactory for sustained intravenous therapy.

Conclusions and Summary

1. A total of 20 (67 per cent) of the 30 patients with shock accompanying myocardial infarction recovered from the episodes of shock under continuous intravenous norepinephrine therapy. Sixteen (53 per cent) recovered completely and were later discharged, while four died of other causes subsequent to the therapy. This is apparently a significant reduction in the fatality rate from reported series of comparable cases in which various forms of intermittent therapy had been used.

2. The average dose of norepinephrine required to elevate and sustain the blood pressure was 7.5 micrograms per minute, although optimal response in different patients was generally obtained with doses varying from 1.5 to 25 micrograms per minute. Rarely do patients respond to higher doses if 25 micrograms per minute proves unavailing; however, in isolated instances doses as high as 150 micrograms per minute have been found necessary. Hence these larger doses should be tried before concluding that the patient is refractory to the treatment.

3. Complications were not unduly consequential, considering the serious nature of the condition under treatment. Varying degrees of tissue necrosis may result from extravasation of norepinephrine into the subcutaneous tissues, however this has not warranted interdicting the therapy. Phlebitis and venous spasm had no significant influence on recovery. No instance was observed suggesting the precipitation or aggravation of congestive heart failure by norepinephrine. In one patient with complete heart block, ventricular tachycardia developed during the administration of large doses (150 micrograms per minute). Further observations of the effects of such doses in comparable cases are necessary to determine the existence of a causal relationship.

4. Renal plasma flow was diminished and glomerular filtration rate essentially unchanged by infusion of norepinephrine. No sequel of renal damage was demonstrated following prolonged therapy. The resultant satisfactory level of blood pressure, as compared with that in the shock state, improves total renal function as evidenced by the prompt increase of urine flow.

5. The continuous administration of this pressor agent with the attendant high percentage of recovery suggests a modification of previous concepts of "irreversible" shock. The artificial maintenance of blood pressures by this means apparently permits the organism to survive a critical period until the natural mechanisms for maintaining the blood pressure are resumed. This restitution was more often abrupt than gradual and occurred from several hours to five and one-half days after starting therapy.

6. The damage to the heart and other vital organs from shock persistent longer than three hours as well as from recurrent episodes of severe hypotension is illustrated by the greater mortality of such cases even with norepinephrine therapy. It is suggested that the early use of intravenous norepinephrine drip therapy in shock accompanying myocardial infarction may demonstrate even further the life saving potential of this drug.

Sumario Español

Se presenta un estudio clínico de la influencia del uso continuo de norepinefrina intravenosa en la terapia del choque que acompaña el

infarto del miocardio. La reducción significativa en la mortalidad inmediata y eventual usualmente asociada con esta condición se discute. Las complicaciones se definen, y un posible primer caso se informa de taquicardia ventricular desarrollándose en presencia de un bloqueo cardíaco completo durante la administración de grandes dosis de norepinefrina.

REFERENCES

[1] HELLERSTEIN, H. K., BROFMAN, B. L., AND CASKEY, W. H.: Shock accompanying myocardial infarction: treatment with pressor amines. Am. Heart J. **44:** 407, 1952.

[2] GOLDENBERG, M.: Adrenal medullary function. Am. J. Med. **10:** 627, 1951.

[3] WAKIM, K. G., AND ESSEX, H. G.: Comparison of the circulatory effects of epinephrine and norepinephrine. Circulation **5:** 370, 1952.

[4] SAYEN, J. J., ET AL.: Favorable effects of *l*-norepinephrine on experimental localized ischemia of myocardium. Proc. 44th Meeting Am. Soc. Clin. Investigation. May 5, 1952. P. 49 (abstr.).

[5] GOLDENBERG, M., PINES, K. L., BALDWIN, E. F., GREENE, D. G., AND ROH, C. E.: The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

[6] SENSENBACH, W., MADISON, L., AND OCHS, L.: A comparison of the effects of *l*-norepinephrine, synthetic *l*-epinephrine, and USP epinephrine upon cerebral blood flow and metabolism in man. J. Clin. Investigation **32:** 226, 1953.

[7] NATHONSON, M. H., AND MILLER, H.: The action of norepinephrine and of epinephrine on the ventricular rate of heart block. Am. Heart J. **40:** 374, 1950.

[8] SMYTHE, C. M., NICKEL, J. F., AND BRADLEY, S. E.: The effect of epinephrine (USP), *l*-epinephrine, and *l*-norepinephrine on glomerular filtration rate, renal plasma flow, and the urinary excretion of sodium, potassium, and water in normal man. J. Clin. Investigation **31:** 499, 1952.

[9] SAMPSON, J. J., KALMANSOHN, R. B., KLINGHOFFER, K. A., AND FRIEDMAN, M.: Sodium and chloride retention following myocardial infarction. Proc. First Internat. Cardiol. Congress, Paris. Vol. 2, Sept. 7, 1950.

[10] SOSKIN, S.: Physiologic basis for the therapeutic effects of cortisone. Rev. Gastroenter. **19:** 10, 1952.

[11] KURLAND, G. S., AND FREEDBERG, A. S.: Potentiating effect of ACTH and cortisone on pressor response to intravenous infusion of *l*-norepinephrine. Proc. Soc. Exper. Biol. & Med. **78:** 28, 1951.

[12] GARB, S., AND CHENOWETH, M. B.: Studies on hydrocarbon-epinephrine induced ventricular fibrillation. J. Pharmacol. & Exper. Therap. **94:** 12, 1948.

[13] NICKEL, J. F., SMYTHE, C. M., AND BRADLEY, S. E.: Effect of pressor agents on renal water and electrolyte excretion in man. Federation Proc. **11:** 113, 1952.

[14] SELZER, A.: The hypotensive state following acute myocardial infarction. 1. Clinical observations. Am. Heart J. **44:** 1, 1952.

[15] WIGGERS, C. J.: Myocardial depression in shock. Am. Heart J. **33:** 633, 1947.

[16] FINK, T. R., D'ANGIO, C. J., AND BILOON, S.: Clinical study of shock following myocardial infarction. J.A.M.A. **151:** 1163, 1953.

[17] CORDAY, E., SPRITZLER, R., KRUEGER, H. E., BERGMAN, H. C., AND PRINZMETAL, M.: Experimentally produced coronary artery insufficiency. Proc. Third Interamerican Cardiological Congress. June, 1948.

[18] SAMPSON, J. J., AND SINGER, I. M.: Plasma and blood infusion following myocardial infarction. Am. Heart J. **38:** 54, 1949.

[19] GRIFFITH, C. G., WALLACE, W. B., COCHRAN, B., NERLICH, W. E., AND FRASHER, W. G.: A study in the management of shock associated with acute myocardial infarction. Twenty-sixth Scientific Session, American Heart Assoc., Atlantic City, N. J., April, 1953.

[20] KAPPERT, A.: Clinical response of human beings to *l*-norepinephrine and its clinical applicability. Acta cardiol. **5:** 121, 1950.

[21] MILLER, A. J., AND BAKER, L. A.: *L*-arterenol in treatment of shock due to myocardial infarction. Arch. Int. Med. **89:** 591, 1952.

[22] KURLAND, G. S., AND MALACH, M.: The clinical use of norepinephrine in the treatment of shock accompanying myocardial infarction and other causes. New England J. Med. **247:** 383, 1952.

[23] MILLER, A. J., SHIFRIN, A., KAPLAN, B. M., GOLD, H., BILLINGS, A., AND KATZ, L. N.: Arterenol in treatment of shock. J.A.M.A. **152:** 1198, 1953.

Clinical Evaluation of Combined Hydrogenated Ergot Alkaloids (Hydergine) in Arterial Hypertension

With Special Reference to Their Action in Central Manifestations

By RALPH M. TANDOWSKY, M.D.

One hundred patients suffering from sustained arterial hypertension were studied over a period of two years during which time the action of parenterally administered hydrogenated ergot alkaloids (Hydergine) constituted the main drug therapy. An immediate transient reduction of both the arterial blood pressure and the pulse rate was demonstrated in over 80 per cent of the entire group within a period of two hours. The average reduction in systolic and diastolic pressure was 36 mm. and 12 mm., respectively, and the pulse rate was reduced 6 beats per minute. Of interest was a group of 22 patients presenting evidence of early central vascular derangement in whom these alkaloids seemed to accomplish their best therapeutic action and possibly aborted what may have been a sustained cerebral accident. Untoward effects were minimal because of rapid dissipation of the drug, and its use in all types of hypertensive disease was deemed safe in the recommended dosage

IN the evaluation of depressor drugs for the palliation of arterial hypertension the selective action of each must be given prime consideration. The syndrome of arterial hypertension is due to the action of a pressor substance, the origin and composition of which may vary as may its strength and choice of effector. Stoll and Hofman[1] first demonstrated three alkaloids contained in ergotoxin, namely; ergocornine, ergokriptine and ergocrystine. They found that one of the double bonds of the lysergic acid component contained in each could easily be hydrogenated. Later, Rothlin[2, 3, 4] and others found that these hydrogenated alkaloids were stable and had selective properties so far as the circulatory system was concerned. These consisted of central vasodilator effect, in the main, and a sympatholytic or adrenolytic effect peripherally.

Recent studies by Barcroft, Konzett and Swan[5] have shown that these alkaloids have little effect on the arterial blood pressure of normal subjects but cause a significant fall in the pressure in hypertensives, particularly in those whose increased pressure is of central origin. They concluded that the vasodilatation brought about was mainly due to inhibition of the vasomotor center with minimal action due to peripheral block at the nerve endings. They found that these alkaloids left the human circulation very rapidly. Gibbs[6] demonstrated a reduction in the arterial blood pressure of 50 hypertensive patients by Hydergine; in 11 the retinal arterioles presented an appreciable dilatation within 10 minutes after injection. He also found a diminished response to the cold-pressor test. Gibbs also pointed out that the subjective symptoms in almost one half of his series were relieved. Inasmuch as these alkaloids act mainly on the vasomotor centers, the probability of their influence on the cerebral circulation must be considered. Using the nitrous oxide method of Kety and Schmidt, J. H. Hafkenschiel and coworkers[7] demonstrated a significant decrease in the vascular resistance of hypertensive patients, using one of these alkaloids, and although the blood flow

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Hydergine supplied by Sandoz Pharmaceuticals; it consists of equal parts of dihydroergocornine, dihydroergocrystine and dihydroergokriptine.

remained constant, the blood pressure decreased.

First mention of their action in the presence of cerebral vascular disturbances was made by Strauss.[8] In a subsequent publication he reported 23 cases of hypertension with cerebral manifestations of which 21 were benefited by this therapy. Lasch[9] published the case history of a hypertensive patient whose cerebral symptoms quickly disappeared after the use of hydrogenated ergot alkaloids. Gross, Leuterer and Matthiessen[10] treated early cases of apoplexy with Hydergine and infiltration of the stellate ganglia with procaine once or twice weekly with satisfactory results. The hydrogenated ergot alkaloids lower the blood pressure by depressing the vasoconstrictor centers and by stimulating the vasodilator centers. In addition, they also stimulate the vagus center, slowing the heart rate. Although they are adrenolytic their action on the peripheral ganglia is felt to be minimal. Clinical observation has shown that they act most effectively when the sodium content of the blood stream is not excessive. For this reason their use in the presence of congestive heart failure and in the nephrotic syndrome may not be impressive.[11, 12] Because these ergot derivatives reduce blood pressure by action on the vascular centers it was felt that they are best suited for the treatment of hypertension of central origin.

The appearance during the course of hypertension of many subjective and objective manifestations of cerebral origin, which at times assume the magnitude of a cerebral crisis, offers a potential field of study best suited to the hydrogenated ergot alkaloids. As yet a close correlation of these symptoms with the height of arterial pressure has not been made. Inasmuch as these drugs have relieved many of these symptoms from time to time,[13] it was felt that a study laying particular emphasis on this phase of Hydergine action was warranted.

Procedure of a Study

Among a group of 100 patients suffering from sustained arterial hypertension it was found that 22 presented themselves with manifestations of early central vascular derangement complicating their hypertension. This group complained of intractable headache experienced most frequently at night or upon arising, sudden aphasia, hemiplegia of short duration, convulsive seizures, tinnitus, syncope, sudden loss of memory, dizziness, irritability, extreme restlessness and insomnia. Some patients of this group were treated for relief of these disturbing symptoms primarily rather than for the routine palliation of their hypertension. Examination disclosed that the severity of these symptoms did not always go hand in hand with the height of the arterial blood pressure. In the remaining 78, few objective manifestations were noted other than elevated arterial blood pressure.

To the group of 22 presenting outstanding evidence of cerebral vascular derangement, Hydergine was given as an emergency measure since the discomfort that these patients experienced necessitated immediate relief and also because previous methods of therapy had failed. The remaining 78 patients received a period of rest of not less than one hour before Hydergine was given. Each first received normal saline intravenously as a control prior to the actual study, after which the blood pressure and pulse were determined at 15-minute intervals for a period of two hours. In the 22 with cerebral manifestations, normal saline controls were likewise instituted as soon as opportunity presented itself. The saline controls were given under the same prevailing circumstances as the Hydergine. Each then received 0.3 mg. of Hydergine diluted with saline intravenously. Comparison was made of the subjective and objective manifestations prior to and after the drug was given at 15-minute intervals for a period of two hours after which time maintenance therapy was instituted within six hours. At the completion of the study four tablets, each containing 1 mg. of Hydergine, were given either orally or sublingually but were found to be ineffectual in appreciably lowering the blood pressure or pulse rate or in relieving the subjective manifestations present. Ambulatory and maintenance care was then instituted by the use of Hydergine subcutaneously or intramuscularly in dosage of 0.3 mg. once or twice daily for a period of from two weeks to one year. These patients were seen at one- to two-week intervals at which time the blood pressure, pulse rate and subjective manifestations were checked. Of the group presenting cerebral manifestations, maintenance therapy was conducted in a similar manner after emergency therapy until it was felt that the drug had been given a fair chance. Previously instituted medication for the relief of cerebral manifestations was investigated and charted. During the course of ambulatory therapy, normal saline was given from time to time in lieu of Hydergine for additional control study.

Results of Study

This group consisted of 44 female and 56 male patients with an average age of 51 and 56 years, respectively. In a number of those in

TABLE 1.—*The Effect of Parenterally Administered Hydergine (CCK-179) in Arterial Hypertension with Central Manifestations*

Case Age Sex	Diagnosis and Complications	Cerebral and Neurologic Manif. and Duration	Previous Medication and Result	Control Studies and Effect	Effect 0.3 mg. Hydergine I.V.			Comment and Clinical Follow-Up
					Blood Pressure and Pulse		Clinical Effect on Cerebral Manifestations	
					Rest.	M.H.E.		
N. S. 56 M.	Essent. hypertens., syphilis	Head., oc., hemipl., lt., deep reflex., lt., absent flac. paral., lt.	Nitrites, sedation. Result none	Deleted	240/140 96	160/100 80	Normal function and relief of headache in 10 minutes	Free from cerebral manif. for 6 months
N. C. 60 F.	Malig. nephro., b.br. block, lt., cor. scl.	Head., fr. and oc., disturb. vision, reflex. exag., restless	Sedation, physiotherapy, aspirin, I.V. glucose. Sl. and temp. relief	Saline I.V. None	220/130 82	180/110 80	Complete relief in 20 minutes	Symptoms returned 2 hours after medication. After 3 months patient maintained on 3 I.M. injections weekly
A. R. 64 M.	Essent., hypertens., congest. ht. fail., mild	Anesthes., tingling lt. arm and leg, weak. lt. arm, mental confus., deep reflex., exag., lt., speech imped. 4 hrs. dur.	Methium, nitrites, sedation. No relief	Saline I.V. No effect	220/126 78	176/105 76	Complete relief in 1 hour	0.3 mg. I.M. daily for 10 days. Mild sedation and nitrites for seven months. Free from cerebral manifestations
R. B. 46 M.	Essent. hypertens., V.P.C.	Head., fr. and oc., rigid. neck, nausea and vom., restless. 1 hr. dur.	Codeine, aspirin, Dramamine. No relief	None	180/100 80	160/90 82	Slight relief of frontal headache. Expired in 24 hrs.	Autopsy revealed subarachnoid hemorrhage from aneurysm
W. B. 60 F.	Essent. hypertens., diabet., obese	Head., oc., syncope, tingling and pain, rt. arm and leg, reflex. exag., retinitis	Insulin, sedation, veratrum, nitrites. No relief	Saline I.V. No effect	180/110 90	140/90 80	Relief of headache, syncope, arm and leg symptoms in 15 min.	Patient receives 0.3 mg. Hydergine when symptoms return. Average dose 2/week
I. B. 65 M.	Essent. hypertens.	Head., oc., aphasia, mot. and sens. 2 hrs. dur.	No previous medication	None	230/130 88	200/110 78	Relief of sensory aphasia in 12 hrs. Relief headache in 20 min.	Received 0.3 mg. Hydergine daily for 2 months. Partial motor aphasia remained

A. D. 69 F.	Essent. hypertens., rh. ht. dis., aur. fib.	Head., oc., convuls. 60 min. dur., hemipl., rt., aphasia, mot. 1 mo. dur.	No previous medication	None	168/110 88	110/90 78	Relief of convulsions in 2 min.	4 subsequent convulsive seizures each relieved within 5 min. Expired 6 mos. later of cereb. thrombosis
J. B. 81 M.	Artscl. ht. dis.	Aphasia, mot. and sens., convuls. 30 min. dur., stertorous breath.	$MgSO_4$ and glucose, I.V. No effect	Saline I.V. No effect	188/90 66	110/80 66	Complete relief in 35 min.	Free from cerebral manifestations for 14 mos. without medication
A. L. 35 M.	Essent. hypertens., sympathectomy in 1947	Head., oc., giddiness and syncope 2 days dur.	Nitrites, aspirin, oral Hydergine. No effect.	Saline I.V. No effect	230/160 89	190/110 80	Complete relief in 5 min.	0.3 mg. Hydergine I.M. at onset of attacks. Gives relief
J. M. 74 M.	Artscl. ht. dis., cholecystitis	Head., fr., mental confus., weak rt. arm and leg, reflex., exag., rt. 4 hrs. dur.	None	Saline I.V. No effect	190/120 92	162/110 84	Relief of headache and right side weakness within 1 hr.	Patient discharged in 2 days
B. S. 65 F.	Essent. hypertens., myo. infarct, old ant.	Head., oc., insomnia 2 hrs. dur.	Aspirin, sedation	Saline I.V. No effect	205/100 72	160/100 72	Relief of headache in 15 min.	Received 0.3 mg. I.M. daily for 2 wks. with continued relief
I. B. 49 F.	Essent. hypertens., early menopause	Head., oc., vom. and syncope before menses 4 hrs. dur.	Sedation, aspirin. codeine, Dramamine. Sl. relief	Saline I.V. No effect	190/110 92	162/100 72	Complete relief within 15 min.	Treatment repeated each month with excellent results
W. H. 58 M.	Malig., nephro.	Head.. oc. and bipar., tinnitus, reflex., exag. 10 days dur.	Sedation. No relief	Saline I.V. No effect	210/120 96	180/100 80	Relief in 20 min.	Received 0.3 mg. q 12 hrs. for maintenance. Expired in 4 wks. with azotemia

Abbreviations:

bipar.—biparietal
dur.—duration
exag.—exaggerated
flac.—flaccid
fr.—frontal
head.—headache
hemipl.—hemiplegia
imped.—impediment
lt.—left
M.H.E.—maximal hydergine effect
mot.—motor
oc.—occipital
rt.—right
V.P.C.—ventricular premature contractions
vom.—vomiting

TABLE 1.—*Continued*

Case Age Sex	Diagnosis and Complications	Cerebral and Neurologic Manif. and Duration	Previous Medication and Result	Control Studies and Effect	Effect 0.3 mg. Hydergine I.V.			Comment and Clinical Follow-Up
					Blood Pressure and Pulse		Clinical Effect on Cerebral Manifestations	
					Rest.	M.H.E.		
C. J. 48 M.	Essent. hypertens., Tbc., pulmon., myo. infarct, old post.	Head., bipar., nausea, tingling and weak., lt. arm and lt. foot., reflex. exag. 4 hrs. dur.	Codeine, aspirin, Gynergen. No relief	Saline I.V. No effect	250/160 90	200/110 80	Complete relief within 30 min.	Taking 0.3 mg. daily for past 2 yrs. with complete relief
J. G. 40 F.	Angiospast. hypertens., early	Head., oc., giddiness, reflex., deep and superfic. exag. 2 hrs. dur.	Sedation, Methium, nitrites. No result	Saline I.V. No effect	226/120 92	170/100 82	Immediate relief. Relaxation retinal vessels in 15 min.	0.3 mg. daily I.M. for 2 wks. Not followed longer
L. T. 41 F.	Essent. hypertens.	Syncope, disturb. vision, stagger gait, 2 wks. dur.	Sedation. No relief	Saline I.V. No effect	210/120 96	178/110 84	Relief of syncopal attacks	0.3 mg. I.M. for 2 wks. with complete relief
J. L. 50 F.	Essent. hypertens., diabet., menopause	Head., oc. and fr., tingling, weak, lt. arm and lt. leg, reflex., deep, exag., unsteady gait 2 mos. dur.	Nitrites, Estrogen No result	Saline I.V. No effect	210/110 86	180/106 80	Relief of headache in ½ hr. Relief of arm and leg symptoms in 2 wks.	0.3 mg. I.M. every 12 hrs. for 2 wks. Free from cerebral manifestations for 14 mos.

A. D. 34 F.	Malig., nephro., anemia, hypochro.	Head., fr. and oc., nausea, syncope, deep reflex., exag., tremor 3 mos. dur.	No previous treatment. No result	Saline I.V. No effect	240/140 96	160/90 80	Complete relief in 20 min.	B.P. did not drop until 30 min. after I.V. Hydergine 0.3 mg. I.M. daily for 1 wk. gave complete relief
M. R. 56 F.	Essent. hypertens., cor. insuff.	Head., fr., mental confus., loss of memory, deep reflex. exag. 4 hrs. dur.	Nitrites, sedatives, aspirin. Relief of angina	Saline I.V. No effect	190/110 110	168/80 82	Relief of headache and mental symptoms in 30 min.	0.3 mg. I.M. for 2 mos. and Peritrate T.I.D. gave complete relief
T. J. H. 55 M.	Essent. hypertens., cor. insuff., cerebral accident, congest. ht. fail., early	Head., oc. and bipar., tingling and weak. lt. leg, insomnia, disturb. vision, Babinski 3 mos. dur.	Digitalis, rice diet. No relief	Saline I.V. No effect	190/90 90	164/84 82	Relief of headache in 10 min. Lt. leg improved in 1 hr.	0.3 mg. I.M. daily for 2 wks. Headaches relieved. Remaining symptoms obtain
T. W. 52 M.	Essent. hypertens., myo. infarct., old	Head., oc., sudden speech imped., weak. rt. arm and leg, deep reflex., exag. 2 hrs. dur.	Nitrites, sedatives, I.V. glucose. No effect	Saline I.V. No effect	178/110 88	166/90 80	Normal function within 12 hrs.	0.3 mg. I.M. every 12 hrs. for 4 days. Then anticoagulants
H. R. 54 F.	Essent. hypertens., obese	Head., oc., weak., lt. arm and leg, deep reflex. exag. 4 hrs. dur.	Sedatives, nitrites, Methium. Sl. relief	Saline I.V. No effect	188/120 90	168/100 80	Complete relief in 20 min.	0.3 mg. I.M. every 24 hrs. for 6 wks.

the younger age groups with uncomplicated arterial hypertension, the systolic and diastolic blood pressure presented a most drastic reduction, but the average reduction for the entire group was 36 mm. Hg systolic and 12 mm. diastolic. The average reduction of pulse rate was 6 beats per minute. These figures represent the maximal change in the two-hour period of observation following the introduction of the drug into the blood stream. Only two patients of the entire group developed untoward symptoms which were worth noting. One of these developed extreme hypotension and was probably sensitive to the drug; the other became apprehensive and complained of weakness and air hunger. Twenty-four of the entire group complained of nasal stuffiness while six complained of a tingling sensation over the surface of the body following medication. The two patients with notable reactions recovered spontaneously within one half hour without special therapy.

Although one half of the entire group complained of headache from time to time, the special group with cerebral manifestations had severe or intractable headaches and other evidence of cerebral derangement. Their headaches were of a throbbing character, usually occurring in the small hours of the morning and often being severe enough to awaken the patient. There appeared to be no direct relationship between the height of the blood pressure and the occurrence of this discomfort as on some occasions severe headache was present when the blood pressure was no higher than at other times when no headache was noted.

The group of 22 with cerebral manifestations was equally divided between males and females and the average age was 55.8 years. The average reduction of systolic blood pressure was 40.5 mm. Hg and the diastolic reduction was 20.7 mm. within the two-hour period. The average reduction in pulse rate was 9 beats per minute. Many of the group presented more than one symptom suggestive of cerebral vascular impairment.

Of these 22 patients, 14 complained of severe occipital headache, 5 of frontal headache and 3 of severe biparietal headache. Of these, 14 were relieved by intravenous Hydergine within two hours, 1 received partial relief, while the remainder were unaffected. Although a fall in blood pressure was noted it was not necessarily proportional to the relief obtained. Four patients had signs of early left hemiplegia while three presented evidence of early right hemiplegia. In only one of these could a Babinski reflex be demonstrated although a definite alteration of the superficial and deep reflexes was evident in the remaining six. The patient with the positive Babinski reflex had well established hemiplegia of six hours duration when first examined. Six of this group completely recovered within the two hours, and an appreciable reduction in blood pressure was noted in all. In two with left hemiplegia the recovery was dramatic, occurring within a period of 15 minutes after medication was given. Both presented a rapid drop in blood pressure. The one patient with the established Babinski sign was unaffected. Four patients complained of visual disturbances and in all four relief was obtained. Three had evidence of early motor and sensory aphasia. Two recovered within two hours after treatment, while one had partial recovery. The one with tinnitus was relieved within one half hour. The reduction of blood pressure in the foregoing patients was not always proportional to the relief of the symptoms. Of the four patients who complained of nausea and vomiting when first seen, three were relieved within two hours while one lapsed into coma and died, autopsy subsequently demonstrating a ruptured intracranial aneurysm as the cause of death. Of the three patients complaining of giddiness and unsteadiness of gait, two were improved while one was partially improved. Anesthesia and tingling of the extremities was noted in five of this group and four were relieved within two hours. The remaining patient was relieved during the course of two weeks by daily medication. All of the three who appeared to be mentally confused when first examined had clarification of their mental state within two hours. Of the two with convulsive seizures, one was relieved while the other subsequently died. Both patients with intractable insomnia failed to benefit by the ergot alkaloids and required sedation while under observation. In the five

patients with syncopal attacks, four were relieved of this symptom while under treatment, while one was unaffected. In the foregoing patients the drop in blood pressure was moderate but appeared to have no direct relationship to the relief obtained.

Follow-up therapy of daily injections of Hydergine was given to this group with encouraging relief of the subjective manifestations. It was observed that subcutaneous or intramuscular injections had a more prolonged but less dramatic effect on the patient.

Discussion

The action of parenterally administered hydrogenated ergot alkaloids produce an appreciable, transitory drop in the systolic and diastolic blood pressures and pulse rate, the duration of which seldom exceeded two hours. For this reason it was felt that their use would be impractical for the routine palliation of hypertensive disease, particularly in ambulatory patients. Their use orally has not proved to be effective in the treatment of hypertension. In the presence of early and impending cerebral complications, however, their action has been shown to be beneficial and in some instances, the author feels, possibly averted what might have been a serious cerebral accident. These drugs, parenterally administered, seem harmless in the dosage recommended due to their rapid elimination.

The first patient observed in this group was given this drug with the hope of quickly lowering the blood pressure, and little consideration was given at the time to the beneficial effect that would occur to the cerebral circulation. The left hemiplegia completely disappeared within 15 minutes after the injection of 0.3 mg. of Hydergine intravenously. It was felt that this hemiplegia was possibly of a reversible nature and was not due to actual cerebral hemorrhage but to a sudden disturbance of the cerebral circulation which in turn produced cerebral anoxia with subsequent paralysis.

The headaches which were such prominent symptoms apparently began after the onset of hypertension but without definite relationship to the level of the arterial blood pressure. Some headaches were migrainous in character, not unlike those reported by Schottstaedt and Sokolow,[15] and appeared to be directly related to a state of emotional tension. It is probable that in some instances, however, a decreased contractile power of the cerebral arterioles, which did not produce discomfort when the blood pressure was normal, resulted in painful distention of the vessel wall when the pressure was elevated. In these, Hydergine possibly gave relief by its regulatory action on the cerebral vessels.

The dizziness, vertigo and giddiness which was encountered was not of the violent type associated with vomiting, complete loss of equilibrium and nystagmus. There seemed to be no correlation between the severity of the vertigo, the age of the patient or the degree and duration of hypertension. It was felt that this symptom could be accounted for, at least in part, by emotional instability. The mode of action of the hydrogenated alkaloids in this and other manifestations of cerebral derangement seen in this series of patients is not known and no possible explanation will be ventured at this time.

Summary

Although Hydergine administered parenterally produces a transient reduction in arterial blood pressure and pulse rate chiefly through a central action, the drug was not shown to be of practical value for the control of ambulatory hypertensives. This study has demonstrated a valuable therapeutic place for these alkaloids in the abolition and relief of certain cerebral manifestations complicating the hypertensive state. The quick abolition of these manifestations may possibly avert organic complications of the central nervous system in at least some hypertensives. Toxic manifestations of these alkaloids are so rare and of so minor a degree as to offer no contraindication to their use parenterally.

Conclusions

1. Combined hydrogenated ergot alkaloids (Hydergine) administered parenterally in a dosage of 0.3 mg. produced a transient reduction in both systolic and diastolic blood pressure and pulse rate.

2. These alkaloids have proven to be of value in the alleviation of early cerebral manifestations complicating arterial hypertension and in some instance apparently averted what may have been a serious organic complication.

3. Their mechanism of action in the presence of cerebral manifestations has been briefly discussed and evaluated.

4. Because of their rapid dissipation when given by the parenteral route, it is felt that untoward symptoms from these alkaloids are minimal and that they may be given without hesitation to hypertensive patients.

Sumario Español

Un estudio clínico de cien pacientes sufriendo con hipertensión arterial sostenida fué hecho por un termino de dos años durante los cuales la acción de la administración parentérica de los alcaloides hidrogenados del cornezuelo de centeno (Hydergine) constituyó la terapia principal. Una reducción transitoria inmediata en presión arterial y el puslo se demostró en 80 por ciento de todo el grupo en un período de dos horas. El promedio de reducción en presión sistólica y diastólica fué de 36 mm. y 12 mm., respectivamente, y el pulso se redujo en 6 pulsaciones por minuto. De interés fué un grupo de 22 pacientes que presentaban evidencia de desarreglo vascular central en que los alcaloides parecieron efectuar su acción terapéutica mayor y posiblemente abortaron lo que hubiera sido un accidente cerebro-vascular. Los efectos indeseables fueron mínimos debido a la disipación rápida de la droga, y el uso de la droga en la dosis recomendada en todos los tipos de enfermedad hipertensa se consideró inocuo.

REFERENCES

[1] Stoll, A., and Hofman, A.: Die Dihydroderivate der natuerlichen linksdrehenden Mutterkoralkaloid. Helvet. chim. acta. **26:** 2070, 1943.

[2] Rothlin, E.: The pharmacology of the natural and dihydrogenated alkaloids of ergot. Bull. schweiz. Akad. med. Wissensch. **2:** 249, 1947.

[3] Blunschli, H. J., and Goetz, R. H.: The effect of ergot derivatives on the circulation in man with special reference to two new hydrogenated compounds (dihydroergotamine and dihydroergocornine). Am. Heart J. **35:** 873, 1948.

[4] Goetz, R. H.: The action of dihydroergocornine on the circulation with special reference to hypertension. Lancet **1:** 510, 1949.

[5] Barcroft, H., Konzett, H., and Swan, H. J. C.: Observations on the action of the hydrogenated alkaloids of the ergotoxine group on the circulation in man. J. Physiol. **112:** 273, 1951.

[6] Gibbs, D. F.: Dihydrogenated alkaloids of ergot in the investigation and treatment of diastolic hypertension. Brit. Heart J. **14:** 77, 1952.

[7a] Hafkenschiel, J. H., Crumpton, C. W., and Moyer, J. H.: The effect of intramuscular dihydroergocornine on the cerebral circulation in normo-tensive patients. J. Pharmacol. & Exper. Therap. **98:** 144, 1950.

[b] —, —, —, and Jeffers, W. A.: The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J. Clin. Investigation **29:** 408, 1950.

[8a] Strauss, H. L.: Klinische Erfahrungen mit Hydergine. Med. Welt. **20:** 113, 1951.

[b] —: Klinische Erfahrungen mit Hydergine. Therapiewoche **2:** 562, 1952.

[9] Lasch, F.: Zur Frage der Blutdruckwirkung des Hydergine. Munch. med. Wchnschr. **94:** 1325, 1952.

[10] Gross, D., Leuterer, W., and Matthiessen, G.: Aktive Apoplexiebehandlung. Munch. med. Wchnschr. **94:** 1734, 1952.

[11] Personal experiences of the author over the past three years.

[12] Personal experiences of the author over the past three years.

[13] Tandowsky, R. M.: Clinical effect of dihydroergocornine methanesulphonate (DHO-180) in arterial hypertension. A preliminary report. Circulation **1:** 686, 1950.

[14] Fishberg, A. M.: The Effects of Arterial Hypertension on the Brain (as quoted by Page, I. H. and Corcoran, A. C.). Hypertension. Chicago, Year Book Publishers, 1945.

[15] Schottstaedt, M. F., and Sokolow, M.: The natural history and course of hypertension with papilledema (malignant hypertension). Am. Heart J. **45:** 331, 1953.

Studies on the Effect of Exercise on Cardiovascular Function

I. Cardiac Output and Mean Circulation Time

By Carleton B. Chapman, M.D. and Robert S. Fraser, M.D.

For technical reasons, the measurement of cardiac output during brisk walking is difficult. By using a slight modification of the Hamilton dye-dilution method, such measurements, and measurements of mean circulation time, were made at rest and at the end of a moderate work load in normal subjects. A motor-driven treadmill was used for the exercise. It was found that the cardiac output increases 1.7 to 1.9 times and the mean circulation time decreases about 34 per cent in normal young men and women after a 10 minute walk at 3 miles per hour and 5 per cent grade.

RESTING measurements of cardiovascular function in patients with asymptomatic heart disease are often perfectly normal and may not serve to differentiate such patients from normal individuals. For this reason, various forms of exercise tests have come into use in an attempt to uncover latent functional incapacity, but certain technical difficulties have been encountered in designing such tests. With regard to cardiac output, few available methods lend themselves readily to studies involving the usual forms of exercise such as walking or running. Grollman's acetylene method has been employed in this situation[1, 2] but some doubt exists, however justifiable, that the technic is valid at high output levels. There are obvious difficulties in connection with using the direct Fick procedure when subjects are walking or running, although it has been successfully applied in other, less physiologic forms of exercise.[3, 4]

The type of exercise employed is also of some consequence. Ideally, one should use a technic to which most subjects are already accustomed and in which the influence of training is reduced to a minimum. If the method is to be applied not merely to healthy individuals but to diseased subjects as well, the work load must be set at a fairly conservative level. On the other hand, it must be adjusted so that measurable circulatory change is induced, whether the subject be well or diseased. Finally, measurements must be made before and during, not after, the exercise, the latter having been maintained long enough to permit the attainment of a relatively steady physiologic state.

The following studies were carried out in the hope of developing a technic that meets most, if not all, these requirements, and of obtaining quantitative information concerning the hemodynamic response of the normal subject to exercise.

Method

The dye-curve technic for measuring cardiac output, as described by Hamilton,[5] was chosen as the most suitable method for present purposes. The sequence followed in the experiments is shown in table 1. In-lying needles were eliminated by the use of polyethylene catheters. For injection of the dye, a PE-90 catheter (inside diameter 0.86 mm., outside 1.27 mm.) was introduced into the median basilic vein through a 15 gauge needle, the puncture site having previously been anesthetized. The catheter was then advanced about 30 cm. into the vein toward the heart and was taped in place. The external end was fitted with an adapter and a three-way stopcock. This accomplished, the guiding needle was withdrawn and allowed to remain on the catheter between the puncture site and the adapter. For collection of arterial blood samples, a PE-50 catheter (inside diameter 0.58 mm., outside 0.97 mm.) was introduced into the brachial artery of the other arm through a thin-walled 18 gauge needle, the puncture site and the tissues around the artery having previously been liberally infiltrated with procaine. It was found that the catheter can usually be intro-

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TABLE 1.—*Sequence of Events, Showing Approximate Time Intervals, in Experimental Procedure*

Time in Minutes	Event
00:00	Subject in bed
10:00	Catheters installed
30:00	Dye injected
to	
30:40	Arterial samples collected
38:00	Subject on treadmill
40:00	Begin exercise, 3 m.p.h., at 5% grade
50:00	Dye injected
to	
50:40	Arterial samples collected
52:00	Stop exercise

duced without difficulty, although at times resistance is encountered in spite of the presence of vigorous, pulsatile blood flow from the open needle. The catheter was advanced about 5 cm. into the artery and the 18 gauge needle withdrawn entirely. The catheter was then carefully taped in place. A 22 gauge needle was inserted into the external end of the catheter and a three-way stopcock attached to the needle. Both venous and arterial catheters were kept filled with heparinized saline solution when not in use for injection of dye or collection of blood. The insertion of the catheters usually occasioned the subjects no discomfort whatever, but occasionally they complained of a slight aching sensation as the needle entered the artery.

Evans blue dye (T-1824) was injected through the venous catheter at zero time from a syringe calibrated to deliver a known amount of dye (2.0 cc. of a 0.5 per cent solution) at the end of the venous catheter. Less than one second was required for the injection.

Arterial blood samples were collected at two-second intervals from the arterial catheter. Flow from the catheter was not pulsatile, owing to its small internal diameter, but proceeded in a drop-by-drop manner. In order to insure the collection of adequate samples during the two-second intervals, a special collecting device, employing a vacuum to speed flow, was used. The device converts intermittent to steady flow and is described in full elsewhere.[6]

A motor-driven treadmill was used for the exercise. Subjects walked on it for 10 minutes at a speed of 3.0 miles per hour and at a 5 per cent grade. This level of exercise corresponds to an average oxygen uptake of 1214 cc. per minute and imposes no particular difficulty on normal subjects leading sedentary lives.

The usual colorimetric method of estimation of dye concentration was modified in the following way: 0.1 cc. of heparinized whole blood was diluted to 1.0 cc. total volume with a normal saline solution and was centrifuged in a Hellige tube. The supernatant diluted plasma was then analyzed for dye content in an Evelyn colorimeter at 620 millimicrons, using a special microadapter.[7]

Use of whole blood for the analyses, instead of serum or plasma, necessitated a change in the usual method of calculating the factor for conversion of density readings to milligrams of dye (K factor). Since the dye is distributed solely in the plasma fraction of whole blood, it is necessary to take the hematocrit reading into account in making the calculation. Known solutions of dye in heparinized whole blood were made up in the usual way, and 0.9 cc. normal saline solution was added to 0.1 cc. aliquots. The diluted blood was then centrifuged for 10 minutes at 2,000 revolutions per minute. The Evelyn colorimetric reading was obtained as for an ordinary sample. The K factor was calculated as *density reading/amount of dye in supernatant volume*. Thus, for a known solution containing 0.299 mg. dye per 5 cc., the calculation is as follows:

Hematocrit	=	50.08 per cent
Amount plasma in 5 cc. blood	=	2.5 cc.
Volume dye solution added	=	0.06 cc.
Total liquid	=	2.56 cc.
Concentration dye per cc.	=	0.117 mg.
Amount plasma per 0.1 cc. blood	=	0.05 cc.
Total dye in 0.1 cc. blood	=	0.0058 mg.
Density reading	=	0.434

Once the K factor is determined for a given lot of dye, it is not necessary to recalculate it for each individual subject unless the hematocrit reading is well outside the normal range. K factors, calculated in the above manner, for hematocrit readings ranging from 40 to 51 per cent were within less than 1 per cent of each other, owing to the large plasma dilution factor (about 16:1). Nor is the normal increase in hematocrit as a result of exercise (from 45.3 ± 2.3 per cent at rest to 47.4 ± 2.4 per cent during exercise) large enough to introduce significant error.

Dye curves were constructed by plotting density readings against time in seconds (fig. 1). The terminal portion of the curve, and the point at which it crossed the baseline, were determined by plotting values between the peak of the curve and the beginning of recirculation on semilog paper. A straight line was fitted to these points and the requisite terminal values were read from it. The area of the curve was determined by planimetry and was used for the calculation of mean dye concentration and mean circulation time. More specifically, the latter was defined as the time taken by one-half of the dye to pass the sampling point; it was obtained by determining the point in time at which a line dividing the area under the curve in half intersected the baseline.

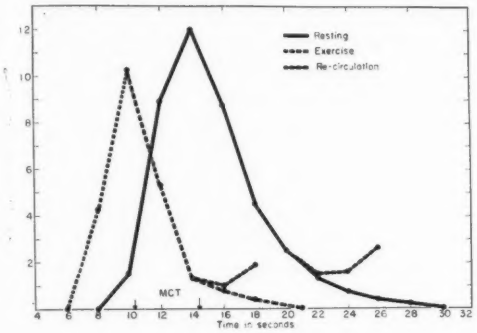

FIG. 1.—Sample dye curves, at rest and during exercise, showing the extrapolated values after the beginning of recirculation.

To calculate cardiac output, the mean density reading obtained by planimetry (total area divided by duration of curve) from the dye curves, was divided by the K factor and the result multiplied by 10,000 to obtain mean concentration of dye per liter of blood. The value was then inserted into the formula:

$$\textit{Cardiac output in liters/minute} = \frac{60 \times \textit{total amount of dye injected}}{\textit{mean concentration dye per liter} \times \textit{duration of curve in seconds}}$$

The subjects used for the study were in good health and had no evidence of cardiovascular disease. They were fasting at the time of testing. There were 11 women, aged 22 to 30 (average 24.2), and 23 men, aged 18 to 39 (average 25.2).

RESULTS

The complete data are set out in tables 2 and 3. The resting figures are comparable with those obtained by other workers using the dye-curve method. For example, the resting figure for cardiac output obtained by Asmussen and Nielsen[2] was 6.86 ± 2.1 liters per minute, the corresponding figure in the present study being 6.91 ± 1.03 liters per minute The value reported by Ring and co-workers,[8] using a method very similar to our own, was somewhat lower (6.44 ± 4.3 liters per minute). Figures given by other workers for the cardiac index[9, 10] vary from 3.2 ± 0.2 to 3.8 ± 0.3 liters per minute per square meter. Our value for the cardiac index (in young men) is 3.63 ± 0.59 liters per minute per square meter of body surface area.

TABLE 2.—*Cardiac Output, Cardiac Index, and Mean Circulation Time at Rest and during Exercise in 23 Normal Young Men*

Subject	Age	Resting			Exercise		
		CO	CI	MCT	CO	CI	MCT
K. W.	25	5.18	2.88	22.4			
G. M.	23	7.57	4.05	17.5	10.86	5.81	9.5
R. K.	19	6.58	4.09	15.0	9.41	5.84	12.8
W. K.	20	5.43	2.70	23.4			
J. G.	18	8.03	4.67	22.4	9.06	5.27	10.2
F. G.	27	6.45	3.26	15.8	15.46	7.81	10.6
J. D.	19	9.19	5.11	17.4	11.75	6.53	9.9
J. D.	19	6.39	3.29	17.2	9.84	5.07	13.3
S. K.	20	6.32	3.49	17.5	7.29	4.03	9.8
T. M.	25	8.31	4.18	15.1	12.46	6.26	12.8
J. E.	22	6.69	3.56	18.6			
J. T.	21	8.89	4.42	15.9	19.92	9.91	17.9
D. S.	29	6.61	3.63	21.7	9.26	5.09	17.4
E. S.	30	7.32	3.50	17.0	12.31	5.89	12.4
E. G.	22				12.27	6.32	12.5
F. D.	29	7.09	3.65	16.0	11.61	5.98	10.6
P. A.	22	7.03	3.70	14.3	8.85	4.66	12.4
W. G.	19	6.45	3.39	17.6	11.36	5.98	11.0
J. L.	24	5.28	2.56	21.0	14.13	6.76	12.7
W. S.	32	6.15	3.20	17.9	15.44	8.04	10.6
R. M.	39	6.51	3.26	14.8	17.84	8.92	10.7
D. H.	38	6.72	3.48	24.3	11.97	6.20	13.8
R. G.	38	7.84	3.77	16.8	12.40	5.96	10.2
Mean....	25.2	6.91	3.63	18.2	12.17	6.32	12.1
S.D.....		±1.03	±0.59	±3.0	±3.07	±1.37	±2.2

In relative terms, the cardiac output in the men increased 1.76 times the resting value during exercise, the corresponding figure for women being 1.89. There was wide variation in response to exercise, however, from individual to individual. In one man, the cardiac output increased only 1.13 times the resting value, and in one woman, at the other extreme, the increase was over fourfold.

Mean circulation time decreased consistently during exercise. In terms of per cent of the resting value, the average decrease for the men was 33.4 and for the women it was 35.7.

DISCUSSION

From the practical point of view, the dye curve technic is more suitable for measurement of cardiac output during exercise than any of the available methods. It does not require special cooperation on the part of the subject, as does the acetylene method, and

TABLE 3.—*Cardiac Output, Cardiac Index, and Mean Circulation Time at Rest and during Exercise in 11 Normal Young Women*

Subject	Age	Resting			Exercise		
		CO	CI	MCT	CO	CI	MCT
P. B.	24	5.29	3.08	16.6	8.96	5.21	11.5
P. S.	22	5.59	3.49	16.3	23.84	14.90	9.6
J. B.	25	5.27	3.44	13.8	9.34	6.10	10.6
C. L.	24	7.01	4.67	10.2	8.93	5.95	7.3
A. M.	22	4.00	2.16	18.6	11.81	6.38	8.5
C. E.	22	4.82	3.11	14.2	7.88	5.08	9.5
I. M.	26	7.11	4.18	13.4	9.19	5.41	8.6
E. H.	24	4.32	2.81	20.2	7.43	4.83	10.0
E. A.	23	5.77	3.54	14.7	10.74	6.59	10.4
M. G.	24	4.68	3.00	16.5	7.78	4.99	11.0
Mean....	24.2	5.64	3.50	15.4	10.66	6.60	9.9
S.D.....		±1.24	±0.78	±2.7	±4.49	±2.73	±1.0

does not require measurement of oxygen consumption as do both the acetylene and direct Fick procedures. It also avoids the necessity for catheterization of the heart, a technic that might involve considerable risk to the subject in experiments of this type. Since the validity of the dye curve method, both at rest and during exercise, now seems to be well established,[2, 11, 12, 13] it is difficult to sustain an objection to its use in appropriate situations. Its application in the present study was not particularly troublesome technically, but required a special collection device, similar to that described by Ring, and associates,[8] and a slight modification of the usual method of colorimetric analysis, the latter permitting use of small samples of heparinized whole blood. The other alternative to the method used is the oximetric technic developed by Wood and colleagues.[14, 15] Theoretically, this technic is the best available for recording dye curves, since it follows changes in dye concentration more precisely than does serial sampling of arterial blood. In addition, the necessary analytic work is somewhat less. There remains some doubt, however, about the possibility of quantitating curves obtained with the ear oximeter for calculation of cardiac output, although calibration of those obtained with the cuvette oximeter appears to be more satisfactory.[8] The technic still requires arterial puncture and the preparation of blood samples containing known amounts of dye. Moreover, the per cent saturation of arterial blood with oxygen must not be allowed to change appreciably during the determination. For the present study, the serial sampling technic proved to be quite satisfactory, but it must be admitted that a two-second sampling interval may well be too long for use in experiments involving very rapid dye curves. A shorter sampling interval, such as was used by Ring and co-workers, is clearly more desirable. Inspection of the curves obtained at the work loads used in the present study, however, seems to indicate that at this level of work, a two-second sampling interval introduces no great error. Some portion of the curve near the peak may not be registered when the two-second interval is used; this may result in a slightly lower mean concentration of dye and a correspondingly high cardiac output. In fact, however, the mean cardiac output during exercise in our normal subjects is somewhat lower than that reported by other workers using the same method at comparable work loads.[2] Heavier work loads, and faster dye curves, would, of course, necessitate the use of a shorter sampling interval.

The study shows that, at the work load used, the cardiac output during exercise may be almost double the resting output in normal young individuals. The decrease in mean circulation time as a result of exercise was around 34 per cent for both groups and was quantitatively somewhat more predictable than the increase in cardiac output. That there is a definite, though rough, inverse correlation between increase in cardiac output, on the one hand, and decrease in mean circulation time, on the other, seems certain. The present data, however, are not suitable for proving the existence of such a relationship. Successive experiments, in the same subjects and using increasing work loads, are needed for the purpose.

Because of the wide variation in response of the cardiac output to exercise in normal individuals, normal standards are difficult to construct. It would, therefore, be hazardous to compare results of the test in a single individual with those obtained by the same test

the group of normals. Comparison of groups of individuals who have cardiovascular disease with normal groups, on the other hand, is possible and the results of such a comparison will be presented in a future paper.

Conclusions

1. The dye-curve technic is readily applicable to the study of changes in cardiac output and mean circulation time produced by exercise in the human being.

2. By applying the technic to normal subjects before and at the end of a 10-minute walk on a motor driven treadmill running at 3 miles per hour and set at a 5 per cent grade, it was found that the exercise causes the cardiac output to increase about 1.7 times in men and 1.9 times in women.

3. The mean circulation time, under the same conditions, decreases about 34 per cent in both groups of normal subjects.

Addendum

The circulation times as given are median, not true mean, values. As pointed out by Hamilton and associates,[5] the true mean circulation time corresponds to the point representing the center of gravity of the curve, and not to the point that divides it into two halves. Recalculation of the data, using Hamilton's equation, shows that in the present work the mean and median circulation times are almost, but not quite, identical. Correct mean circulation times for the subjects tested will be presented in part III of the present series of studies.

Acknowledgment

We wish to express our sincere thanks to Miss Phyllis Waldsmith, Laboratory Technologist, without whose technical skill and unfailing good nature the work could not have been done.

Sumario Español

Por razones técnicas, la medida del trabajo cardíaco durante un andar acelerado es dificil. Por medio de una ligera modificación del método de dilución de tinte de Hamilton, estas medidas al igual que tiempos promedio de circulación fueron determinados durante el descanso y al final de ejercicio moderado en sujetos normales. El ejercicio se hizo en un molino de rueda de andar movido a motor. Se encontró que el trabajo cardíaco aumenta de 1.7 a 1.9 veces y el tiempo de circulación promedio disminuye como 34 por ciento en hombres jovenes normales y mujeres luego de una caminata de 10 minutos a 3 millas por hora y una pendiente de 5 por ciento.

References

[1] Nielsen, H. E.: Clinical investigations into the cardiac output of patients with compensated heart disease during rest and during muscular work. Acta med. scandinav. **91:** 223, 1937.

[2] Asmussen, E., and Nielsen, M.: The cardiac output in rest and work determined simultaneously by the acetylene and the dye injection methods. Acta physiol. scandinav. **27:** 217, 1953.

[3] Hickam, J. B., and Cargill, W. H.: The effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[4] Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G.: The effect of exercise on circulatory dynamics of normal individuals. J. Applied Physiol. **3:** 439, 1951.

[5] Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. Am. J. Physiol. **99:** 534, 1932.

[6] Archibald, H. T., Fraser, R., and Chapman, C. B.: A collecting device for obtaining blood samples at various intervals from an intra-arterial catheter. Science, In press, 1953.

[7] Freier, E. F., and Larson, E. A.: A micro-adapter for the Evelyn macro colorimeter. J. Lab. & Clin. Med. **33:** 1594, 1948.

[8] Ring, G. C., Oppenheimer, J. J., Baier, H., Sokalchuk, A., Bell, L. L., Ichtiarowa, L. D., Ellis, D. W., Lynch, P. R., and Shapiro, L. F.: Wood's cuvette oximeter for measurement of dye concentration in blood. J. Applied Physiol. **5:** 43, 1952.

[9] Doyle, J. T., Wilson, J. S., Lépine, C., and Warren, J. V.: An evaluation of the measurement of the cardiac output and of the so-called pulmonary blood volume by the dye-dilution method. J. Lab. & Clin. Med. **41:** 29, 1953.

[10] Beard, E. F., Wood, E. H., and Clagett, O. T.: Study of hemodynamics in coarctation of the aorta using dye diluation and direct intra-arterial pressure recording methods. J. Lab. & Clin. Med. **38:** 858, 1951.

[11] Hamilton, W. F., Riley, R. L., Attyah, A. M.,

COURNAND, A., FOWELL, D. M., HIMMELSTEIN, A., NOBLE, R. P., REMINGTON, J. W., RICHARDS, D. W., JR., WHEELER, N. C., AND WITHAM, A. C.: Comparison of the Fick and dye injection methods of measuring the cardiac output in man. Am. J. Physiol. **153:** 309, 1948.

[12] WERKO, L., LAGERLOF, H., BUCHT, H., WEHLE, B., AND HOLMGREN, A.: Comparison of the Fick and Hamilton methods for the determination of cardiac output in man. Scandinav. J. Clin. & Lab. Investigation **1:** 109, 1949.

[13] NEWMAN, E., MERRELL, M., GENECIN, A., MONGE, C., MILNOR, W. R., AND MCKEEVER W. P.: The dye dilution method for describing the central circulation. An analysis of factors shaping the time-concentration curves. Circulation **4:** 735, 1951.

[14] BEARD, E. F., AND WOOD, E. H.: Estimation of cardiac output by the dye dilution method with an ear oximeter. J. Applied Physiol. **4:** 177, 1951.

[15] NICHOLSON, J. W. III, AND WOOD, E. H.: Estimation of cardiac output and Evans blue space in man, using an oximeter. J. Lab. & Clin. Med. **38:** 588, 1951.

Comparison of Various Vascular Beds in Man

Their Responses to a Simple Vasodilator Stimulus

By WALTER REDISCH, M.D., LOTHAR WERTHEIMER, M.D., CLAUDE DELISLE, M.D., AND J. MURRAY STEELE, M.D., WITH THE TECHNICAL ASSISTANCE OF HARVARD REITER, B.S.

Blood flow to the extremities and kidneys was measured simultaneously in normal subjects, hypertensive patients and patients with obliterative arterial disease of the lower extremities. The latter group showed diminished basal flow in the lower extremities, increased basal flow in the upper extremities, and a delayed and diminished response to reflex heating, compared with the normal and hypertensive subjects. In all three groups, the increase in extremity blood flow was regularly accompanied by a concomitant decrease in renal blood flow. No significant change in arterial pressure was observed.

ATTEMPTS to correlate rate of regional blood flow with clinical manifestations of arterial disease have so far not been too successful for several reasons. The methods employable in man are limited and, by necessity, indirect; base line data have been difficult to obtain, and knowledge of the interplay between various vascular beds is fragmentary. It was believed, therefore, that simultaneous measurements of blood flow to the skin and muscle of an extremity and of a visceral organ such as the kidney might give promise of a better understanding of shifts of blood flow under physiologic and pharmacologic stimuli. The present study concerns the response of kidney and extremity to the simple vasodilator stimulus devised by Gibbon and Landis.[20]

METHODS

Of the many methods available for estimating blood flow to the extremities of man,[1–10] plethysmography was chosen as the most accurate and most direct in spite of its known difficulties.[11–14] A rather complete description of the apparatus is deemed necessary since the principles involved have only been used heretofore on very small objects such as finger tips or toe tips.[15–17]

1. Blood Flow to the Extremities

An air transmission plethysmograph has been developed,* using a strain gauge to measure volume changes in terms of very small pressure changes (3 or 4 mm. Hg), too small to affect blood flow. Readable pulse curves from parts as large as foot plus leg have been obtained with this instrument. The stopcock arrangement on the operation board (fig. 1) provides for prompt connection from plethysmograph to strain-gauge, plethysmograph to air, strain-gauge to recorder and strain-gauge to air. There are also connecting stopcocks for sudden venous occlusion, using a large reservoir in which the air is kept at the desired pressure (30 mm. Hg for foot, hand, or hand and forearm; 40 mm. Hg for foot and leg). The apparatus has two channels permitting simultaneous recording of plethysmographic changes from two limbs if desired. The direction from which the impulse enters the strain-gauge determines the direction of the slope; one of the channels produces a rising, the other one a falling slope on the graph. Calibration of the pressure changes in terms of volume is made by injecting 5 ml. of air before each single set of three recordings of blood flow. The instrument proved to be quite sensitive and the return to the baseline after release of occlusion is exact. The sensitivity of the recording device permits use of a large dead space, making it possible to keep conditions within the chamber quite constant, as evidenced by continuous temperature

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Dr. Wertheimer is a Fellow of the Public Health Research Institute of New York City, Inc.

Dr. Delisle is a Fellow of the Federal and Provincial Government of Canada.

* We wish to thank Dr. Joseph Greenspan of Process Instruments, Brooklyn, New York, and Dr. Silvester Liotta, Professor of Physical Chemistry at City College, New York, for their invaluable help and advice.

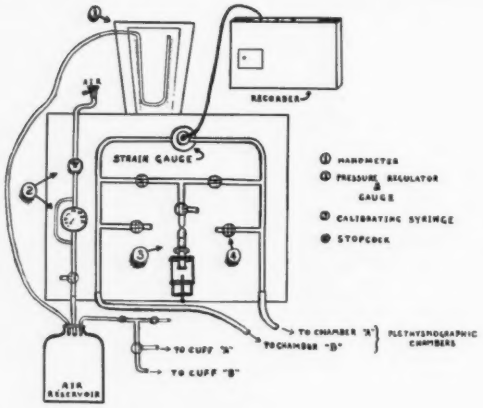


FIG. 1. View of controls of operation board of strain gauge plethysmograph.

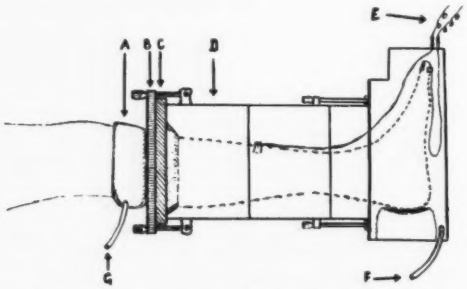


FIG. 2. Plethysmographic chamber with thermocouples in place. *A* = occlusion cuff; *B* = metal flange; *C* = rubber cuff; *D* = plastic chamber; *E* = thermocouples to toe and leg; *F* = connecting part with strain gauge; *G* = connection of cuff with reservoir.

recording (fig. 2). In turn, the large size of the dead space requires great constancy of environmental conditions as afforded by the constant temperature room.

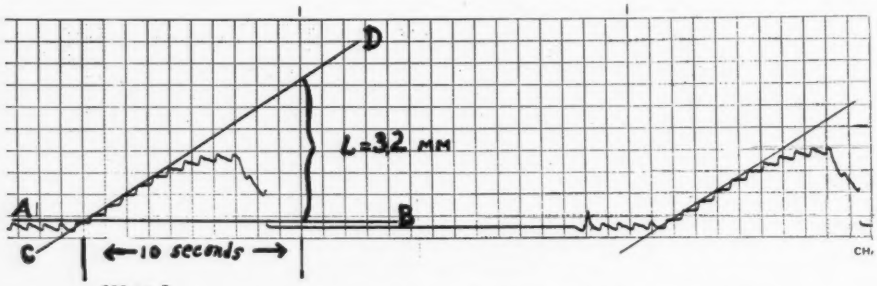
For sealing the limb within the plastic case, greased foam rubber covered with sheet rubber and a rubber cuff for direct contact with the skin is used. Leaks in the apparatus are easily detected by injecting a small amount of air (5 ml.) and waiting for 30 seconds to see whether the displaced baseline remains horizontal.

Good seals have been obtained without evident obstruction of the veins, and responses to venous occlusion have been prompt. After sudden venous occlusion proximal to the plethysmograph, the linear portion of the rising slope of the curve is used to calculate the rate of blood flow (fig. 3).

The volume of the part of the limb enclosed in the chamber is calculated from the effect which known volumes placed within the chamber have on the deflection caused by the addition of 5 ml. of air. The larger the volume of the limb, the smaller the remaining volume in the chamber and the greater the deflection. From the time scale a distance equivalent to 10 seconds is measured on the baseline and a perpendicular (*L*) erected at this point. Blood flow in ml. per minute in 100 ml. of tissue is calculated from the formula:

$$\frac{600 \times L}{K \times V} = \textit{Blood flow (ml. per minute per 100 ml. of tissue)}$$

wherein *L* is the perpendicular rise in slope in centimeters during 10 seconds, *K* is the calibration constant of the recording apparatus in millimeters deflection per milliliter of change in volume, and *V* is the volume of the enclosed limb segment in milliliters. Changes in blood flow through the arm and hand or leg and foot taken together and then through the hand or foot alone are used to calculate



Formula: $\frac{600 \times L}{K \times V}$; $L = 3.2$ cm.; $K = 0.5$ cm. per cubic centimeter; $V = 500$ cc.

$$\frac{600 \times 3.2}{0.5 \times 500} = 7.68 \text{ ml. per 100 cc. of tissue per minute}$$

FIG. 3. Sample of tracing representing the change of volume of the extremity after venous occlusion. On this channel to the strain gauge, the descending slope indicates increase in volume of limb. Note the exact return to baseline after release of occlusion.

ly difference the rate of flow through forearms and legs.

When measuring the blood flow through an extremity one actually is dealing with three vascular beds rather than with one: the skin, the deeper soft tissues, mostly muscle, and the bones. No attempt was made to estimate the blood flow to the bones.

To obtain evidence as to what portion of total blood flow went to muscle and what portion to skin, estimation of the ratio of skin to muscle in the arms and legs and in the hands and feet was attempted.* Anteroposterior and lateral soft tissue x-ray films of the extremities of nine people of different build and sex were made and from measurements of the areas of skin and of muscle, estimates of the relative volume of skin and muscle were made. The approximations for skin-muscle ratios ranged in leg and forearm from 0.23 to 0.55, averaging 0.36 for the leg, 0.31 for the forearm, and in hand and foot from 3.0 to 5.0, averaging 4.1 for the hand and 4.0 for the foot. These ratios indicate that plethysmographic records of hands and feet represent predominantly blood flow through the skin, while those of the forearms and legs represent predominantly blood flow through the deeper tissues (except bone), that is, mainly muscle.

2. Renal Blood Flow

Changes in renal plasma flow were measured by the technic of maintaining a constant infusion of sodium para-aminohippurate. Arterial blood samples were taken from an indwelling 21-gauge Cournand needle inserted into a brachial artery. Three samples were taken at 15-minute intervals to establish a baseline, and three more at the height of vasodilatation in the extremities as indicated by surface temperature and plethysmographic readings. For simplicity the assumption was made that the rate of infusion of the substance was the same as the rate of excretion in the urine, an assumption justified by the work of Berger, Farber and Earle.[18] In following this assumption the clearance calculation can be stated as $C = IV/P$ where C is the clearance of para-aminohippurate in milliliters per minute and corresponds to the renal plasma flow, I is the concentration of para-aminohippurate in the infusion in milligrams per milliliter, V is the rate of infusion in milliliters per minute and P is the plasma concentration of para-aminohippurate in milligrams per milliliter. Para-aminohippurate in a trichloracetic acid filtrate was deacetylated by heating for one hour in a tenth normal hydrochloric acid solution.[18] The solution was then diazotized and coupled, using the Marshall-Bratton[19] procedure. Renal blood flow was calculated from plasma flow on the basis of concurrently determined hematocrits.

* We wish to thank Dr. Louis Bergman, Associate Professor of Anatomy at New York University College of Medicine, for his friendly advice.

Procedures

The principle upon which we have relied in testing vasomotor responses is that vasodilator agents and procedures should be tested against a mild vasoconstrictor stimulus and vice versa. The baseline data for testing vasodilator responses have all been obtained in an environment of 20 C. and 50 to 55 per cent humidity, conditions which afford a mild vasoconstrictor stimulus. After adaptation to the environment has been ascertained to have taken place (surface temperature being recorded quasi-continually on a six-channel Speedomax), heating of the body is induced by the Gibbon-Landis procedure[20] by heating an extremity in a water bath at 44 to 45 C., maintained for 45 minutes in normal reactors. In cases of marked obliterative arteriosclerosis where a delayed reaction is encountered, the procedure is extended until skin temperature has leveled off but never for longer than 90 minutes; there may be an extremely rare case in whom no reaction can be elicited.

This type of experiment, measuring blood flow to the extremities and to the kidneys simultaneously, has been performed on 11 normal subjects, 6 patients with sustained essential hypertension and 10 patients with obliterative arterial disease of the lower extremities.

Results

As is well known, heating the body produces reflex vasodilatation in the nonimmersed extremities. Essentially, this effect was regularly observed in all three types of patients studied. The average changes observed in the three groups are given in table 1.

Simultaneous decrease in renal blood flow occurred with the increase in flow to the extremities. The maximal decrease in renal blood flow varied from 10 per cent to 13 per cent and coincided roughly in time with the

Table 1.—*Influence of a Standard Vasodilator Stimulus (Landis-Gibbon Test) on the Blood Flow of the Extremities under Basal Conditions after Adaptation to an Environment of 20 C.*

	Foot		Leg and Foot		Hand		Forearm and Hand	
	Basal Flow	Maximal Flow	Basal Flow	Maximal Flow	Basal Flow	Maximal Flow	Basal Flow	Maximal Flow
Normals	1.1	8.6	1.1	3.1	1.6	19.0	1.7	7.4
Arteriosclerotics	0.3	3.6	1.8	2.8	2.5	15.1	1.1	7.9
Hypertensives	0.6	11.8	1.3	4.3	1.2	13.2	0.6	5.1

Figures represent averages expressed in cc. of blood per 100 cc. of tissue per minute.

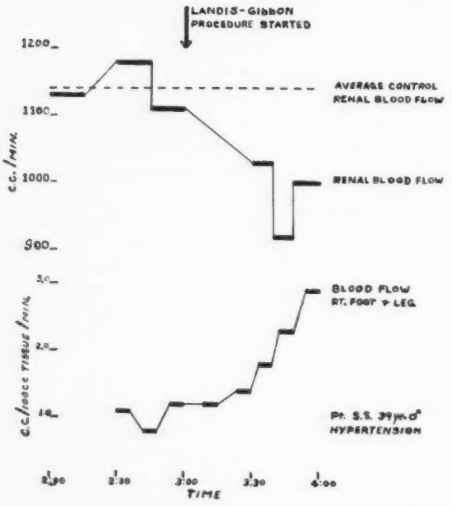


FIG. 4. The graph shows the peripheral (leg) and visceral (kidney) response to the standard Landis-Gibbon procedure.

maximal increase in blood flow to the extremities (fig. 4).

Arterial pressure was measured throughout the experiment. In no instance was there any significant change in either systolic or diastolic pressure.

DISCUSSION

Several points of interest emerge from these studies. One was that patients with obliterative arteriosclerosis had in general lower basal flows to the feet and higher ones to the hands than had the normals and the hypertensive patients. These findings might be interpreted as an indication that the hands compensate for the inability of the feet to meet demands for elimination of heat. Such an interpretation finds support in the fact that skin temperature curves show that in contrast to normals[21] the hands of patients with obliterative arteriosclerosis in the lower extremities take over in part the task of coarse adjustment to the environment.

Our findings corroborate those of Page[22] who showed that renal flow decreased when the body was heated by diathermy. The work of Radigan and Robinson,[23] who produced evidence that renal blood flow in a hot environment was considerably lower than in a cool environment and that exercise regularly lowered blood flow through the kidney, is also of interest in this connection. Barklay and co-workers[24] and Chapman and associates[25] showed likewise that heavy exercise reduced renal blood flow considerably. It seems clear, therefore, that whenever blood flow to areas of the extremities where glomi are abundant increases appreciably in order to meet a demand for increased heat dissipation, renal blood flow decreases. The inverse response of different vascular beds to a simple vasodilator procedure suggests that vasodilator drugs might well be studied with regard to regional effects on the vascular tree.

The shift in blood flow from visceral (renal) to peripheral (extremity) vascular channels took place in the absence of any significant change in arterial pressure.

SUMMARY

1. No significant difference was found between normal persons and hypertensive patients in either their basal extremity flow or in their response to reflex heating. People with obliterative arterial disease of the lower extremities show diminished basal flow in the diseased parts compensated by increased basal flow in the upper extremities, and their response to reflex heating is delayed and diminished.

2. In a cool environment increase in blood flow to the lower extremities in all three groups occasioned by reflex heating (Gibbon-Landis test)[20] was regularly accompanied by a decrease in renal blood flow of from 10 per cent to 13 per cent.

3. No significant change in arterial pressure was observed during the experiments.

SUMARIO ESPAÑOL

La circulación de las extremidades y los riñones fué medida simultáneamente en sujetos normales, pacientes hipertensos y pacientes con enfermedad oclusiva arterial de las extremidades inferiores. El último grupo mostró una circulación basal en las extremidades inferiores disminuida, aumentada en las extremidades superiores, y una respuesta retardada y disminuida al reflejo térmico, com-

parado con los sujetos normales e hipertensos. En los tres grupos el incremento en circulación de la extremidad fué regularmente acompañado por un decremento concomitante en circulación renal. No se observó cambio significativo alguno en presión arterial.

REFERENCES

[1] STEWART, G. N.: Studies on the circulation in man. I. The measurement of the blood flow in the hands. Heart **3:** 33, 1911.

[2] MENDLOWITZ, M.: Observations on the calorimetric method for measuring digital blood flow. Angiology **1:** 247, 1950.

[3] —, AND ABEL, H. A.: Quantitative blood flow measured calorimetrically in the human toe in normal subjects and in patients with residua of trench foot and frostbite. Am. Heart J. **39:** 1, 1950.

[4] SHEARD, CH., KEGERREIS, R., AND BROWN, G. E.: Calorimetric studies of the extremities. I. Theory and practice of methods applicable to such investigation. J. Clin. Investigation **3:** 327 1926. II. Experimental aspects and procedures. J. Clin. Investigation **3:** 357, 1926. III. Clinical data in normal and pathological subjects with localized vascular disease. J. Clin. Investigation **3:** 369, 1926.

[5] FISHBACK, D. B., GUTTMAN, S. A., AND ABRAMSON, E. B.: An objective method of determining blood velocity (fluorescein method). Am. J. M. Sc. **203:** 535, 1942.

[6] LANGE, K., AND BOYD, L. J.: The use of fluorescein to determine the adequacy of the circulation. M. Clin. North America **26:** 943, 1942.

[7] CRISMAN, J. M., AND FUHRMAN, F. A.: Studies in gangrene following cold injury. IV. Use of fluorescein as indicator of local blood flow; distribution of fluorescein in body fluids after intravenous injection. J. Clin. Investigation. **26:** 259, 1947.

[8] SMITH, B. C., AND QUIMBY, E. H.: Use of radioactive sodium in the study of peripheral vascular disease. Ann. Surg. **125:** 360, 1947.

[9] TRENOUTH, S. M.: Blood oxygen studies in vascular disease. Thesis, Graduate School of the University of Minnesota, Minneapolis, Minn. March 1936.

[10] VEAL, J. R., AND MCCORD, W. M.: Blood oxygen changes in intermittent claudication. Proc. Soc. Exper. Biol. & Med. **37:** 692, 1938.

[11] LEWIS, TH., AND GRANT, R.: Observations upon reactive hyperemia. Heart **12:** 73, 1925.

[12] PRINZMETAL, M. A., AND WILSON, C.: The nature of the peripheral resistance in arterial hypertension with special reference to the vasomotor system. J. Clin. Investigation **15:** 63, 1936.

[13] ABRAMSON, D. I.: Vascular responses in the extremities of man in health and disease. Chicago, University of Chicago Press, 1944.

[14] WISE, C.: Fluid displacement and plethysmograph. In Potter, Van R., ed.: Methods in Medical Research. Chicago, Year Book Publishers, 1948, Vol. 1, p. 182.

[15] GRUNDFEST, H., HAY, J. J., AND FEITELBERG, S.: A strain gauge recorder for physiological volume, pressure and deformation measurements. Science **101:** 255, 1945.

[16] BURCH, G. E.: A new sensitive portable plethysmograph. Am. Heart J. **33:** 48, 1947.

[17] MEGIBOW, R. S., AND FEITELBERG, S.: Application of microplethysmography to diagnosis of patent ductus arteriosus and coarctation of the aorta. Am. J. Med. **11:** 798, 1948.

[18] BERGER, E. Y., FARBER, S. J., AND EARLE, D. P., JR.: Comparison of the constant infusion and urine collection methods for the measurement of renal function. J. Clin. Investigation **27:** 710, 1948.

[19] BRATTON, A. C., AND MARSHALL, E. K.: A new coupling component for sulfonamide determination. J. Biol. Chem. **128:** 537, 1939.

[20] GIBBON, J. H., JR., AND LANDIS, E. M.: Vasodilatation in lower extremities in response to immersing the forearms in warm water. J. Clin. Investigation **11:** 1019, 1932.

[21] REDISCH, W., SCHECKMAN, E., AND STEELE, J. M.: Skin temperature response of normal human subjects to various conditions. Circulation **6:** 862, 1952.

[22] PAGE, I. H.: In Bell, E. T.: Hypertension. Minneapolis, University of Minnesota Press, 1951.

[23] RADIGAN, L. R., AND ROBINSON, J.: Effects of environmental heat stress and exercise. J. Appl. Physiol. **2:** 185, 1949.

[24] BARKLAY, J. A., COOKE, W. T., KENNEY, R. A., AND NUTT, M. E.: The effects of water diuresis and exercise on volume and composition of urine. Am. J. Physiol. **148:** 327, 1947.

[25] CHAPMAN, C. B., HENSCHEL, A., MINCKLER, J., FORSGREN, A., AND KEYS, A.: The effects of exercise on renal plasma flow in normal male subjects. J. Clin. Investigation **27:** 639, 1948.

Comparison of Visceral and Peripheral Vascular Beds in Hypertensive Patients

Their Responses to Various "Hypotensive" Drugs

By WALTER REDISCH, M.D., LOTHAR WERTHEIMER, M.D., CLAUDE DELISLE, M.D., AND J. MURRAY STEELE, M.D., WITH THE TECHNICAL ASSISTANCE OF LOUISA MULCARE, B.S.

The responses of the kidney and the lower extremities to single intravenous doses of six "hypotensive" drugs were measured in eight patients diagnosed as having essential hypertension. Use of Hexamethonium, Ilidar and Hydergine was followed by increase in the flow to the extremity and simultaneous decrease in renal blood flow. In contrast, the administration of Apresoline was followed by decrease in flow to the extremity and an increase in renal blood flow. Regitine produced no significant change in either. After the administration of protoveratrine, renal blood flow decreased but a significant change in blood flow to the extremity was not observed. Changes in arterial pressure which occurred with some of the drugs were not correlated with the changes in blood flow to the extremities or to the kidney.

WHEN studying the effect of reflex heating (Gibbon-Landis procedure[1]) by simultaneously measuring the rate of blood flow in different vascular beds in normal subjects and arteriosclerotic and hypertensive patients, it was found that the procedure affected inversely the blood flow to the kidneys (a decrease) and to the lower extremity (an increase) in all three groups.[2] These observations suggested that the regional effects on the vascular tree of hypotensive and vasodilator drugs studied with the same technics might be of interest. This paper deals with the responses of the vascular beds of the kidney and the lower extremity to single intravenous doses of hypotensive drugs in patients with essential hypertension.

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Dr. Wertheimer is a Fellow of the Public Health Research Institute of the City of New York, Inc.

Dr. Delisle is a Fellow of the Federal and Provincial Government of Canada.

METHODS

Direct plethysmography with an air transmission apparatus which has previously been described in detail[2] was used for measuring blood flow in the extremities.

Changes in renal plasma flow were measured by the technic of maintaining a constant infusion of sodium para-aminohippurate. The assumption was made that the rate of infusion of the substance was the same as the rate of excretion in the urine.[3] Plasma flow was calculated by dividing the rate of infusion by the plasma level. Blood flow was then calculated on the basis of the hematocrit and renal plasma flow.

The base lines for testing responses have all been obtained in an environment of 20 C. and 50 to 55 per cent humidity. These conditions afford a mild vasoconstrictor stimulus.

Eight patients classified as having "essential hypertension" have been studied. The clinical findings are summarized in table 1. The effects of Apresoline upon the vascular beds of the extremities and the kidneys were also studied in a preliminary way in a patient in whom unilateral subtotal sympathectomy had been performed and in two nonhypertensive paraplegic subjects with traumatic transection of the cord, one at T-4 and one at a somewhat lower level.[25]

The following six drugs have been used:

1. *Hexamethonium* was given intravenously in dosages of 5 and 10 mg. This drug is capable of blocking both sympathetic and parasympathetic ganglia. The sympathetic blockade is manifested by hypotension, particularly of the postural variety,

TABLE 1.—*Clinical Findings*

Name Age Sex	Type and Duration of Hypertension	Blood Pressure (Base Line)	Hist. of Cerebro-vascular Accident	Hist. of Congest. Fail.	Cardiac Size (X-ray)	Electrocardio-gram	Blood Urea Nitro-gen (*mg. %*)	Urinary Examination	Other Studies or Findings
B. J. 60 M.	Essential 25 yrs.	210/135	None	None	Left vent. enlarg.	Left axis deviation	18.8	Negative	
M. H. 60 F.	Essential 15 yrs.	220/130	5 yrs. before with complete recovery	None	No enlarg.	Left axis deviation	18.3	Negative	Regitine test negative
S. S. 37 M.	Essential 10 yrs.	210/140	None	None	No enlarg.	Left axis deviation	19.2	Negative	
P. W. 64 F.	Essential 10 yrs.	280/140	None	None	Left vent. enlarg., slight	Left axis deviation	13.5	Negative	
C. S. 46 F.	Essential 20 yrs.		None	For 2 yrs., controlled by digitalis	Left vent. enlarg., mod.	Left axis deviation	14.2	Negative	
R. J. 48 M.	Essential 7 yrs.	220/120	Several with complete recovery	None; anginal syndrome present 6 yrs.	Cardiac enlarg., slight	Left axis deviation	14.2	Negative	
O. R. 54 M.	Essential 2 yrs.	200/100	None	None	No enlarg.	No axis deviation	26	Negative	
S. H. 50 F.	Essential 3 yrs.	190/100	None	For 1½ yrs., controlled by digitalis	Left vent. enlarg.	Left axis deviation	15.4	Negative	

increase in skin temperature and diminished sweating. Parasympathetic blockade is manifested by a decrease in salivation and gastric secretion, constipation and impaired visual accommodation. Cardiac output is supposed to be either unchanged or slightly decreased.[4-7]

2. *Apresoline* (1-hydrazinophthalazine) was given intravenously in a dosage of 15 mg. This hypotensive agent has been shown to increase renal blood flow, heart rate and cardiac output without increasing cerebral blood flow, and to lower arterial pressure. It has been found to antagonize certain humoral pressor substances and is supposed to block vasopressor reflexes from breathholding and immersion of the hand in ice water.[8-15]

3. *Ilidar* (6-allyl-6,7-dehydro-5 H-dibenzazepine-phosphate) was given intravenously in dosages of 5 and 10 mg. This new drug has been described as a "vasodilator compound with adrenergic blocking action." Green and co-workers have shown that in dogs 1 mg. of Ilidar per kilogram prevented a rise in arterial pressure in response to a subsequent injection of epinephrine.[16] It appeared, therefore, that this compound is capable of completely blocking the usual vasoconstrictor response to epinephrine.

4. *Hydergine*, an equal mixture of three hydrogenated ergot alkaloids, namely, dihydroergocornine, dihydroergocrystine and dihydroergokryptine, was given intravenously in dosages of 0.6 mg. It is supposed to act centrally on the vasomotor center and peripherally to a small extent by blocking sympathetic vasoconstrictor impulses in the

TABLE 2.—*Average Changes Observed in Response to Reflex Heating and to Six "Hypotensive" Drugs*

	Skin Temp. Toes Max. Change	Blood Flow Foot and Leg		Renal Blood Flow	Change in Arterial Pressure		Pulse Rate Change
		Basal Flow	Maximal Response		Systolic	Diastolic	
	°C	*ml./100 ml./min.*		*ml./min.*	*mm./Hg*	*mm./Hg*	*per min.*
Heat	+5.8	1.3	4.3	−12%	0	0	+22
Hexamethonium	+5.6	0.9	2.4	−12%	−57	−21	+13
Protoveratrine	+1.7	0.8	0.8	−7%	−16	−10	−4
Ilidar	+4.1	0.8	2.7	−7%	−21	−5	+3
Hydergine	+3.3	1.2	1.6	−11%	−24	−15	−5
Apresoline	−0.5	0.7	0.4	+37%	−5	−5	+18
Regitine	0	0.9	0.9	0	+4	+5	0

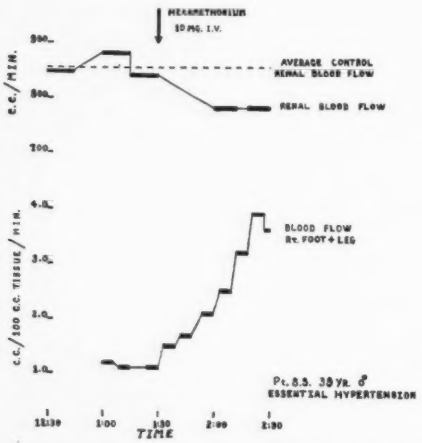

FIG. 1. The graph shows the peripheral (leg) and visceral (kidney) response to hexamethonium.

nerve endings. It produces mild hypotension and bradycardia not abolished by atropine.[17, 18, 19]

5. *Protoveratrine*, the first pure alkaloid from veratrum album shown to have hypotensive properties in man without significant side effects,[20] was given in amounts of 100 to 170 micrograms intravenously. Its depressor effect has been ascribed to the inhibition of pressoreceptors of the carotid sinus in the aortic arch and of a similar vasodepressor reflex pathway arising in the heart itself. Protoveratrine produces marked vagal slowing of the heart which can be effectively blocked by atropine without affecting the depressor effect. Hoobler and co-workers found vasodilatation of the extremities and a slight increase in renal blood flow after administration of protoveratrine. Meilman, however, could not observe any increase in renal blood flow; he did not measure peripheral flow.[20, 21, 22]

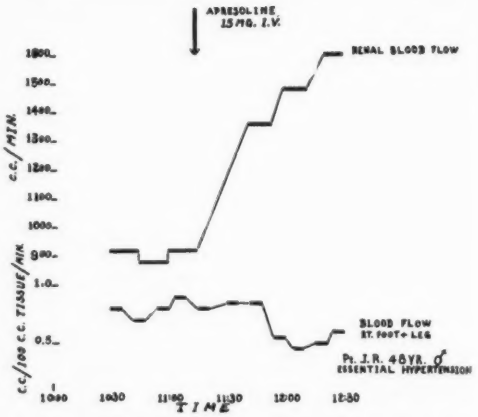

FIG. 2. The graph shows the peripheral (leg) and visceral (kidney) response to Apresoline.

6. *Regitine* (2[(m-hydroxy-N-p-tolylanilino)-methyl]-2-imidazoline methanesulfonate) was given intravenously in a dosage of 5 mg. It is described as a potent sympatholytic drug. Some degree of transient hypotension was seen in a small number of subjects. Regitine at present is used chiefly in the detection of epiniphrine-producing tumors.[23, 24]

RESULTS

Hexamethonium produced a marked increase in skin temperature and extremity flow, a decrease in renal blood flow and a well-marked fall in arterial pressure (table 2, fig. 1).

Apresoline caused a decrease in skin temperature and extremity flow, marked increase in renal blood flow and no significant change in arterial pressure (table 2, fig. 2). It emerged that the interruption of certain nervous pathways alters the response of vascular beds to Apresoline: the two paraplegics showed increase in extremity flow and no change in renal flow; so did the hypertensive on the sympathectomized side, while her normal side reacted as seen in the eight hypertensive subjects who comprise the main body of this study.

Ilidar and Hydergine produced marked increase in skin temperature and extremity flow, moderate decrease in renal flow and a moderate fall in arterial pressure.

Protoveratrine caused no significant change

in skin temperature or extremity flow, moderate decrease in renal flow and a marked fall in arterial pressure.

Regitine produced no significant change in any of the measurements with the dosage used.

Discussion

The inverse effect observed with a simple vasodilator procedure (Gibbon-Landis test) upon different vascular beds has been evident also in the majority of experiments testing the response to hypotensive agents. Increase in blood flow to the periphery was regularly accompanied by decrease in renal blood flow, and increase in renal blood flow was usually accompanied by decrease in extremity flow. Changes in blood flow, both peripheral and visceral, could not be correlated with changes in arterial pressure in these experiments. Bull[26] has just recently stressed that blood pressure changes do not always accompany "circulatory adjustments." In perfusion experiments,[27] changes in pressure between 100 and 170 mm. Hg did not influence renal blood flow. Decrease in renal blood flow has been observed to occur in the absence of any change in blood pressure.[26]

The question as to what mechanisms are responsible for these "circulatory adjustments" remains largely unanswered. Of considerable interest in this connection are certain observations made with Apresoline. It was known that this drug caused marked increase in cardiac output along with a proportionately smaller increase in renal blood flow and also an increase in hepatic blood flow.[28] The fact that in our experiments blood flow to the extremities never participated in this increase and usually even decreased after Apresoline suggests that the vasodilatory effect of this drug (when given intravenously) is chiefly in the visceral regions when the nerve supply is intact.

It is hoped that continuation and extension of the studies on paraplegic, hemiplegic and partially sympathectomized patients may shed some light at least on the neural factors involved in circulatory adjustments between various vascular beds.

Sumario Español

Las respuestas del riñon y las extremidades inferiores a una dosis sencilla intravenosa de seis drogas hipotensivas fueron medidas en ocho pacientes diagnosticados como hipertensos. El uso de Hexamethonium, Ilidar y Hydergine fué seguido por un incremento de circulación en la extremidad y un decremento en la circulación renal. En contraste la administración de apresolina fue seguida por un decremento en circulación de la extremidad y un incremento en circulación renal. Regitine no produjo cambio significativo alguno ni en uno o el otro. Luego de la administración de protoveratrine, la circulación renal disminuyó pero un cambio significativo en circulación de la extremidad no se observó. Cambios en presión arterial que ocurrieron con algunas de las drogas no correlacionaron con los cambios en circulación de la extremidad o el riñon.

Summary

1. Blood flow to the lower extremities and renal blood flow were measured simultaneously in eight patients suffering from essential hypertension, and the responses to single intravenous injections of Hexamethonium, Apresoline, Ilidar, Hydergine, Protoveratrine and Regitine were recorded.

2. Hexamethonium, Ilidar and Hydergine produced increase in extremity flow and decrease in renal blood flow. In contrast, Apresoline caused decrease in extremity flow and increase in renal blood flow. Protoveratrine did not change significantly the blood flow to the extremity, but did lower the renal blood flow. Regitine produced no significant changes in either.

3. There seemed to be no correlation between changes in arterial pressure and changes in blood flow to the regions measured.

4. In the vascular beds measured, the response to Apresoline was markedly altered in two cases of transection of the cord (increase in extremity flow, no change in renal blood flow); the same modification in response was observed on the sympathectomized side of a hypertensive patient who had been subjected to unilateral subtotal sympathectomy.

REFERENCES

[1] GIBBON, J. H., JR., AND LANDIS, E. M.: Vasodilatation in lower extremities in response to immersing the forearms in warm water. J. Clin. Investigation **11:** 1019, 1947.

[2] REDISCH, W., WERTHEIMER, L., DELISLE, C., AND STEELE, J. M.: Comparison of various vascular beds in man; their responses to a simple vasodilator stimulus. Circulation **9:** 63, 1954.

[3] BERGER, E. Y., FARBER, S. J., AND EARLE, D. P., JR.: Comparison of the constant infusion and urine collection methods for the measurement of renal function. J. Clin. Investigation **27:** 710, 1948.

[4] PATON, W. D. M., AND ZAIMIS, E. J.: Pharmacological actions of polymethylene bistrymethylammonium salts. Brit. J. Pharmacol. **4:** 381, 1949.

[5] BURT, C. C., AND GRAHAM, A. J. P.: Pentamethonium and hexamethonium iodide in investigation in peripheral vascular disease and hypertension. Brit. M. J. **1:** 455, 1950.

[6] FREIS, E. D., FINNERTY, F. A., SCHNAPER, H. W., AND JOHNSON, R. L.: The treatment of hypertension with hexamethonium. Circulation **5:** 20, 1952.

[7] MOYER, J. H., HUGGINS, R. A., HANDLEY, C. A., AND MILLS, L. C.: Effect of hexamethonium chloride on cardiovascular and renal hemodynamics and an electrolyte excretion. J. Pharmacol. & Exper. Therap. **106:** 157, 1952.

[8] WILKINSON, E. L., BACKMAN, H., AND HECHT, H. A.: Cardiovascular and renal adjustments to an hypotensive agent, 1-hydrazinophthalazine. J. Clin. Investigation **31:** 872, 1952.

[9] MOYER, J. H., HANDLEY, C. H., AND HUGGINS, R. A.: Pharmadynamic effects of 1-hydrazinophthalazine. J. Pharmacol. & Exper. Therap. **103:** 368, 1951.

[10] JOHNSON, R. L., FREIS, E. D., AND SCHNAPER, H. W.: Clinical evaluation of 1-hydrazinophthalazine (C-5968) in hypertension. Circulation **5:** 833, 1952.

[11] SCHROEDER, H. A.: Control of hypertension. Arch. Int. Med. **89:** 523, 1952.

[12] TAYLOR, R. D., PAGE, I. H., AND CORCORAN, A. C.: Hormonal neurogenic vasopressor mechanism. Arch. Int. Med. **88:** 1, 1951.

[13] FREIS, E. D., AND FINNERTY, F. H.: Suppression of vasomotor reflexes. Proc. Soc. Exper. Biol. & Med. **75:** 23, 1950.

[14] GRIMSON, A. S., CHITTUM, J. R., AND METCALF, B. H.: Action of apresoline on vasomotor reflexes and hypertension. Federation Proc. **9:** 279, 1950.

[15] HAFKENSCHIEL, H., FRIEDLAND, C. K., YOBAGGY, J., AND JEFFERS, W. A.: Cerebral blood flow, vascular resistance, oxygen uptake and oxygen tension in patients with essential hypertension before and after intramuscular administration of 1-hydrazinophthalazine (Apresoline). Am. J. Med. **14:** 509, 1953.

[16] MOORE, P. E., RICHARDSON, A. W., AND GREEN, H. D.: Effects of a new dibenzazepine derivative, RO 2-3248, 6-allyl-6,7-dihydro-5H-dibenz(c,e)azepine phosphate upon the blood flow, the peripheral resistance and the response to injections of epinephrine of the innervated hind limb of the dog. J. Pharmacol. & Exper. Therap. **106:** 14, 1952.

[17] ROTHLIN, E.: Pharmacologie und Klinik der hydrierten Mutterkornalkaloide. Wien. Klin. Wchnschr. **62:** 892, 1950.

[18] BARCROFT, H., KONZETT, H., AND SWAN, H. J. C.: Observations on the action of the hydrogenated alkaloids of the ergotoxine group on the circulation in man. Am. J. Physiol. **112:** 273, 1951.

[19] FREIS, E. D., STANTON, J. R., LITTER, J., CULBERTSON, J. W., HALPERIN, M. H., MOISTER, F. C., AND WILKINS, R. W.: The hemodynamic effects of hypotensive drugs in man. II. Dihydroergocornine. J. Clin. Investigation **28:** 1387, 1949.

[20] —, —, CULBERTSON, J. W., LITTER, J., HALPERIN, M. H., BURNETT, C. H., AND WILKINS, R. W.: The hemodynamic effect of hypotensive drugs in man. I. Veratrum viride. J. Clin. Investigation **28:** 353, 1949.

[21] HOOBLER, S. W., CORLEY, R. W., AND KABZA, T. G.: Effects of Protoveratrine on the circulation in hypertension. J. Clin. Investigation **30:** 651, 1951.

[22] MEILMAN, E.: Clinical studies on veratrum alkaloids. III. The effect of protoveratrine on renal function in man. J. Clin. Investigation **32:** 80, 1953.

[23] MEYER, R., JONKMAN, F. F., CRAVER, B. N., AND GROSS, F.: 17083P—A new imidazoline derivative with marked adrenolytic properties. Proc. Soc. Exper. Biol. & Med. **71:** 70, 1949.

[24] GRIMSON, K. S.: Treatment of pheochromocytoma. J. A. M. A. **140:** 1273, 1949.

[25] STUNKARD, A., WERTHEIMER, L., AND REDISCH, W.: Unpublished data.

[26] BULL, G. M.: The relation of the renal blood flow to the general circulation. In Visceral Circulation, A Ciba Foundation Symposium. Boston 1953. P. 245.

[27] BRULL, L.: In Visceral Circulation. A Ciba Foundation Symposium. Boston, 1953. P. 201.

[28] MOYER, J. H.: Hydrallazine (Apresoline) hydrochloride. Arch. Int. Med. **91:** 419, 1953.

Clinical Appraisal of Intra-arterial Priscoline Therapy in the Management of Peripheral Arterial Diseases

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Priscoline can be given intra-arterially without difficulty. Untoward reactions are infrequent even in older patients. Intra-arterial administration was often effective in patients who did not respond to oral Priscoline. Although maximal vasodilatation may not be achieved by giving Priscoline intra-arterially, the degree of vasodilatation obtained is often adequate for a clinical effect. Results in 250 patients indicate that intra-arterial Priscoline is most useful in the treatment of ischemic rest pain resulting from organic vascular disease. Improvement in exercise tolerance was infrequent. Causalgia, delayed wound healing and ulceration in Reynaud's disease responded favorably in some instances.

ONE of the major objections to the use of chemical sympathetic blockade to produce vasodilatation in the management of peripheral arterial disease has been the inability to confine the effects of the medication to the local vascular bed where vasodilatation is desired. Despite the fact that maximal skin flow can be achieved following the use of intravenous blocking agents,[1, 2] these drugs often produce annoying side effects because of their "generalized" effects, especially in the elderly patient. This, and the repeated failure to obtain a maximal rise in skin temperature following the use of Priscoline by the usual routes of administration, seemed to indicate that there might be a use for the drug when given intra-arterially. This approach has been used for other drugs to a limited extent for many years and intra-arterial Priscoline has been employed by several observers during the past six years.[3-10] While we know from personal communications that many clinicians have followed this therapeutic technic, the method is not widely known. The exact role of intra-arterial Priscoline in the therapy of vascular disease has not as yet been clearly defined, especially since the introduction of other effective blocking agents.

Priscoline (2-benzyl-4,5-imidazoline hydrochloride) exerts its adrenergic blocking effect in the periphery. In addition to blocking responses produced by stimulation of the sympathetic nerves or injection of epinephrine, Priscoline appears to have some direct dilating effect on the vessel wall. The drug is neither necrotizing to tissue nor is it irritating to the vascular endothelium.[11-19]

The peripheral site of action, absence of irritation to the vessel wall, probable local dilating effect, and practical freedom from serious side effects, with proper precautions, makes Priscoline particularly suitable for intra-arterial administration.

METHOD OF ADMINISTRATION

The method of injection into the femoral, radial, or brachial artery is simple, but the technic must be learned in order to avoid technical difficulties, especially since it is one not commonly used by the average physician. Intra-arterial administration is to be carried out with the patient lying down.

The basic technic of injection is as follows: a skin wheal is raised with Novocaine, and through this a finely sharpened 22-gauge needle is inserted into the artery at right angles. The color of the arterial blood, plus pressure transmitted into the syringe, will make clear that the artery has been entered. Good injection sites, where the respective arteries are nearly always readily palpable are: *Femoral Artery*, immediately below Poupart's ligament; *brachial artery*, at superior angle of antecubital fossa just medial to biceps tendon; and *radial artery* at usual wrist site of palpation of pulse.

In our experience, local vasodilatation has been obtained only if Priscoline is injected slowly into the artery over a period of three to five minutes. Because of "spill" into the general circulation, rapid administration produces more generalized effects quite comparable to those following intravenous

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administration. We have found that 2 cc. (50 mg.) is most effective in the majority of cases.

Administration of Priscoline intra-arterially is followed by visible changes in the injected extremity; these occur 15 to 90 seconds after starting the injection. The upper extremity responds considerably faster than the lower, with intense flushing of the forearm and palm occurring within 15 seconds. In the injected lower extremity, piloerection and erythema are usually patchy in the proximal portion of the thigh and become diffuse from the lower third of the thigh distally. Appearance of goose flesh and erythema is followed by visible distention of the superficial veins. Skin temperature and oscillometric excursions may increase, decrease, or remain unaltered, depending upon the patency of the peripheral vessels and the degree of vasoconstriction in the limb being injected. It is of interest to note that intense erythema of the injected extremity may occur without a significant rise in skin temperatures above control levels; likewise, in some of the instances to be cited, pain was relieved by the injection even though skin temperature and pulse amplitude remained unaltered. It is therefore apparent that surface temperature and oscillometric criteria, even under well-controlled conditions, do not necessarily reflect accurately the clinical response. Duration of effect is from one to three hours.

The "adrenolytic" action of Priscoline given intra-arterially can be demonstrated as follows: a wheal in the skin raised with 1:100,000 epinephrine causes the surrounding area to blanch over a diameter of 1 to 1.5 cm. The same amount of epinephrine injected into the skin after 50 to 75 mg. of intra-arterial Priscoline either fails to blanch the skin or the development of the marginal zone of pallor is prevented. Priscoline given in 50 to 75 mg. doses orally or intravenously does not prevent epinephrine-induced blanching.

Since 1948 observations upon the effects of intra-arterial Priscoline have been extended to a group of over 250 patients with known or suspected peripheral vascular disease. Their ages ranged from 18 to 81 years, and many of them had concurrent cardiac and renal disease, diabetes, hypertension, or malignancy.

Over 2,000 intra-arterial injections of Priscoline have been given in this group without serious mishap. Most of the patients have received up to a dozen such injections, often while receiving anticoagulants. One received a mixture of Priscoline and heparin intra-arterially at 24-hour intervals for seven successive days. Six patients have received from 30 to 250 injections each.

The only adverse local effect has been occasional ecchymosis. Bleeding at the injection site has never been troublesome and is readily controlled by simple pressure for one to three minutes. Occasionally periarterial thickening occurred near the site of injection after prolonged therapy. This made repeated injections difficult.

Side effects included mild orthostatic vertigo in about 15 per cent of the patients over 60 years of age. Transient tachycardia and, occasionally, a slight rise or fall in blood pressure were observed in some patients, but these showed no consistent association with vertigo.

Two patients (under treatment for arteriosclerosis obliterans) who had antecedent myocardial infarctions, experienced anginal pain after unduly rapid injection of the drug. Pain began within a few minutes and lasted from 30 minutes to three hours, with complete recovery. Electrocardiographic evidence of myocardial ischemia was obtained during the period of substernal pain in one of these patients. Other patients having known coronary or myocardial disease have tolerated intra-arterial Priscoline, given slowly, without adverse effects.

Four patients developed multiple premature ventricular contractions following rapid injection of Priscoline; none of these, nor the two preceding cases, showed significant hypotension during these episodes. All six are living and are apparently unharmed by these events 14 months after their occurrence.

Results

Normal Individuals

Fifty to 75 mg. of Priscoline given intra-arterially to 10 normal patients produced rises in skin temperatures equal to that following procaine block of a peripheral mixed nerve (table 1).

The rise in skin temperature is accompanied

Table 1.—*Summary of Results in Ten Normal Fasting Subjects under Standard Conditions*

	Priscoline intra-arterially	Peripheral nerve block (procaine)
Change from control temperature	Range +5.4 to +10 C. Average +7.6 C.	Range +6 to +9.8 C. Average +7.9 C.
Maximal digital temperature attained	Range 30.5 to 33.2 C. Average 32.2 C.	Range 30.2 to 33.6 C. Average 32.5 C.

Room temperature 23 C. ±1.

TABLE 2.—*Summary of Skin Temperature Changes in Ten Normal Fasting Subjects under Standard Conditions*

	1st Toe	1st Toe	3rd Finger	Umbilicus	Forehead
	P	C	P		
After 75 mg. Priscoline intra-arterially.....	+7.1 C.	+1.6 C.	+1.3 C.	+0.4 C.	+0.9 C.
After 75 mg. Priscoline intravenously.....	+4.2 C.	+4.2 C.	+3.0 C.	+0.6 C.	+0.9 C.

Room temperature 23 C. ±1.
P, digits on injected side; C, contralateral digits.

by an increase in the volume of pulsations distal to the point of injection. This increase ranges from 50 per cent to 200 per cent and in many instances equals that elicited by procaine block of a peripheral nerve. Studies utilizing the portable venous occlusion plethysmograph to measure skin blood flow demonstrated that intra-arterial Priscoline did not increase blood flow to the same extent as intravenous hexamethonium. The degree of increase, however, was significant although not maximal. These observations have been published elsewhere.[2]

Although slow intra-arterial injection will confine most of the effect to the single extremity, some of the drug reaches the general circulation and measurable skin temperature increases occur in contralateral extremities and elsewhere. Table 2 demonstrates this as well as compares changes in surface temperature when the drug is given intravenously.

It is noted that following intra-arterial administration, the first toe on the injected side shows a 2.9 C. greater rise than with intravenous injection. Likewise, contralateral digits demonstrated significantly less rise following intra-arterial as opposed to intravenous injection, indicating better localization of effect.

Neurovascular Arterial Disease

A. Raynaud's Disease. In seven patients with Raynaud's disease and two with acrosclerosis, severe blanching of the fingers produced by exposure to cold prior to administration of intra-arterial Priscoline could not be produced after its administration.

Indolent ulcers of the fingertips in five of these cases healed after three to five weeks of combined oral and intra-arterial Priscoline therapy, and the intense pain associated with digital ulceration was relieved for progressively longer periods during therapy.

One of the patients in this group had undergone bilateral sympathectomy in 1949; digital ulcers developed two years later. These were associated with intense burning, stinging pain. Oral Priscoline in 150 mg. doses had been administered without improvement, but intra-arterial administration immediately provided relief. Pain disappeared completely as the lesions healed, and such scarring as ultimately resulted was not painful.

All of these patients have been followed for from 6 to 18 month periods, subsequent to intra-arterial therapy, and have remained on oral Priscoline or oral Dibenzyline. There have been some recurrences of blanching following exposure to cold, but there has been no recurrence of ulcers.

Although intra-arterial Priscoline is effective in these cases, most patients with this disease are young, relatively healthy, and without heart disease. They may be treated with other agents such as Hexamethonium during the period when ulceration is present. This drug can be given subcutaneously or intravenously (35 to 50 mg. twice daily). The necessity for intra-arterial administration is thus eliminated and, although a more "generalized" effect is produced by Hexamethonium, the local therapeutic effect is also obtained. If the physician is not fully aware of the effects of Hexamethonium it is much safer to use Priscoline even by the intra-arterial route. Dibenzyline is also effective in some of these cases. This drug may be given orally (10 to 30 mg. four times daily). In the milder cases of Raynaud's disease without ulcerations, oral Dibenzyline, or even oral Priscoline, may produce good results.

B. Painful Neurovascular Disorders. Thirty-

eight patients with painful neurovascular disorders of the "causalgic type" received Priscoline injected into the appropriate artery proximal to the site of pain. Doses ranged from 25 to 75 mg. given over a five-minute period.

This group included eight patients with "minor causalgia" complicating chronic venous insufficiency, six with painful postphlebitic ulcer, six with painful scars, three with meralgia paresthetica, four with posttraumatic pain syndrome following spinal cord injuries, two with shoulder-hand syndrome, two with causalgia of the upper extremities following cerebral vascular accidents, three with postherpetic neuralgia, one with Sudeck's atrophy, and three with residual cold injury.

The results obtained with intra-arterial Priscoline in these patients are difficult to evaluate for several reasons. First, there is some degree of functional overlay in the majority, and as a result it is impossible to determine how much of the improvement represented a response to medication and how much was a response to suggestion. Second, Priscoline administered intra-arterially produces definite sensory effects (warmth and piloerection) and no satisfactory placebo could be found to permit control studies. Lastly, many of the patients were receiving compensation, and it was therefore to their advantage to deny improvement. All these factors must be considered in interpreting the following results. If no relief was obtained, or if severity of symptoms were diminished for only 30 to 60 minutes following injection, the treatment was considered to have failed.

Eighteen patients obtained complete relief of discomfort comparable to the effects of procaine block of the lumbar or stellate ganglia. In eight patients temporary partial relief was obtained; after repeated relapses two had surgical sympathectomies and obtained lasting relief.

Among these patients, relief of longstanding discomfort was occasionally dramatic. One patient with a painful scar of the lower extremity of three years' duration could not tolerate the weight of bedclothes on her leg; Etamon, oral Priscoline, and local infiltration of the scar with procaine had been tried unsuccessfully. After intra-arterial Priscoline, the discomfort disappeared completely and did not return. Another patient, 70 years of age, suffered from a crippling causalgia of her right upper extremity which had persisted for six months after a cerebral vascular accident. Here again, pain was completely and lastingly relieved after one intra-arterial injection of 50 mg. of Priscoline. In all but one case, the pain associated with postphlebitic ulcers (which in some instances had been present as long as six months) disappeared after one or two treatments.

Postherpetic neuralgia responded promptly in one case but was completely unaffected in two others.

The five patients who had antecedent spinal cord injuries obtained no significant degree of relief.

One of the patients with shoulder-hand syndrome was completely asymptomatic after two treatments while the other was unimproved.

The majority of the patients who obtained only partial temporary relief returned at varying intervals for treatment, usually during severe exacerbations of their discomfort, and occasionally obtained some measure of relief.

Many of the patients regarded as failures in this group of 38 were so classified because of variation in, rather than absence of, response to treatment; relief appeared to follow some of the injections but did not occur consistently enough to permit accurate appraisal. It is to be noted that even when relief of pain was not obtained in these patients, intra-arterial Priscoline consistently produced erythema, piloerection, increase in volume of pulsations and skin temperature in the treated extremities.

In comparing the results obtained with intra-arterial Priscoline in causalgic states with those obtained in "post-traumatic causalgia" treated with Hexamethonium and Dibenzyline by other observers,[20] it would appear that these latter agents produce relief of symptoms more consistently. We would agree that these agents appear to be superior to Priscoline in the treatment of "causalgic states." In the occasional patient who cannot tolerate Hexa-

nethonium or Dibenzyline, intra-arterial Priscoline therapy certainly should be tried.

Organic (Occlusive) Arterial Disease

One hundred thirty-one patients with organic arterial disease have received Priscoline intra-arterially, either as a diagnostic or therapeutic procedure. Not a single adverse effect of repeated arterial puncture occurred in this group. There were 65 patients with arteriosclerosis obliterans, 51 with thromboangiitis obliterans, and 12 with sudden arterial occlusion caused by thrombosis or embolism.

A. Arteriosclerosis Obliterans. These patients ranged from 39 to 81 years of age. Twenty-two had concurrent coronary heart disease, four had diabetes mellitus, and four had malignant neoplasms.

The change in the skin temperature of the toe which followed the intra-arterial injection of Priscoline in this group showed the following variations:

In 24 patients, skin temperatures attained almost complete vasodilatation levels of 31 to 33 C. Twenty others attained a somewhat limited increase (1 to 6 C.), with the final temperatures ranging between 22 to 28 C. In 12 patients there occurred no change in skin temperature, even though the foot became pink and the veins visibly distended. Nine others showed a paradoxic fall in skin temperature of the foot. In the proximal portions of these latter extremities, there was unquestionable dilatation of the skin vessels and increase in skin temperature, even though the toes became cooler and paler. Two of the patients in whom this paradoxic response occurred initially showed an elevation of skin temperature of the foot ranging from 3 to 5 C. after several months of intensive treatment with intra-arterial Priscoline.

The most gratifying results following administration of Priscoline intra-arterially occurred in patients with ischemic rest pain. Twenty-five of the patients with arteriosclerosis obliterans were suffering from this type of pain of varying severity. In all instances the pain was of sufficient intensity to interfere with the patient's sleep and to require analgesics, and over two-thirds of these individuals required narcotics at two to four-hour intervals. Eighty per cent of the group obtained permanent relief of rest pain after multiple intra-arterial injections of Priscoline. In many, pain was promptly lessened and requirements for sedation and analgesics diminished after the first injection. Some slept without medication for the first time in several weeks following the initial dose. However, pain frequently returned and repeated injections were necessary before it was completely abolished.

Temporary intensification of pain occasionally followed by relief was noted when the paradoxic lowering of skin temperature occurred after the injection. Relief of pain was not contingent upon a significant rise in skin temperature and was even obtained in patients with areas of superficial gangrene.

Increase in exercise tolerance was attained in only a few of these patients. Even in these it was difficult to ascribe the improvement to the intra-arterial Priscoline. The degree of relief of ischemic rest pain obtained with intra-arterial Priscoline is actually greater than that obtained with hexamethonium and Dibenzyline. This occurs despite the fact that skin blood flow may not be increased to as great a degree by Priscoline.

B. Thromboangiitis Obliterans. Fifty males and one female with thromboangiitis obliterans were studied. They ranged in ages from 18 to 39 years. Disease had been present from one to eight years, and therapy, consisting of postural exercises, reflex heat, vasodilators or sympathectomy, antibiotics, ointments, and soaks had been employed. All had received oral Priscoline. Some of these patients had pain which was so intense and so resistent to treatment that they had consented to undergo amputation to secure relief. Gangrene was present in 26 patients. It involved over 25 per cent of the foot in eight of these, and in the remainder it was confined to one or more digits.

Tobacco was interdicted routinely in all patients with thromboangiitis obliterans. Some of the patients were already abstaining from tobacco when they came under the author's observation. Over one third of the group however, "broke training" with varying frequency

after tobacco was prohibited. Attempts at rigid enforcement of the prohibition met with little success. As a rule, response to treatment was more rapid and gangrene less frequent in the patients who discontinued smoking.

Fourteen patients, including four who had previous sympathectomies, obtained complete lasting relief from pain after intra-arterial Priscoline therapy. These patients required intensive therapy, receiving from one to two injections of 50 to 75 mg. daily over periods from two to four weeks. Ten patients received partial relief. Nine obtained temporary relief ranging from 2 to 36 hours in duration.

Eighteen others in this group had pain of unusual severity, requiring morphine in 16 mg. doses every three to four hours. In the authors' experience only a very small percentage of patients so afflicted could be expected to escape major amputation. Nevertheless, in the group that received intra-arterial Priscoline, only three required subsequent major amputations. Two had transmetatarsal and five had digital amputations. In eight cases gangrenous lesions involving the soft tissues healed completely without surgical intervention. Healing appeared to be accelerated and the duration of hospital stay was shortened by the use of intra-arterial Priscoline.

In the patients with thromboangiitis obliterans, as in those with arteriosclerosis obliterans, there was partial relief of ischemic pain at rest as well as a diminution in the requirements for narcotics. Exercise tolerance, however, was only occasionally increased to a significant degree.

Three patients experienced return of their discomfort several weeks after intra-arterial Priscoline was discontinued despite the fact that the drug was being taken by mouth. Pain was again relieved following the institution of intra-arterial Priscoline therapy.

Results in another group of patients with thromboangiitis obliterans who were treated with hexamethonium and Dibenzyline have been reported elsewhere.[21] Although the degree of release of vasomotor tone and vasodilatation produced by these agents is often greater than that produced by intra-arterial Priscoline, only rarely is a more significant increase in exercise tolerance or pain relief obtained. In some instances, intra-arterial Priscoline produced a more significant increase in blood flow than did oral Dibenzyline. In all cases tested, intravenous hexamethonium produced the most significant increase in skin temperature and blood flow.

C. Sudden Arterial Occlusion (Thrombosis and Embolism). Priscoline by the intra-arterial and oral routes, together with anticoagulant therapy, was employed in the management of 12 patients with sudden arterial occlusion. Sudden closure of the artery was caused by embolism (blood clot) in three, traumatic thrombosis in two, simple thrombosis in three, and sudden thrombosis superimposed on old arteriosclerosis obliterans in the remaining five.

Nine of these patients were not subjected to surgery because they were not presented to us within the period felt to be "optimal" for surgical results. In the remaining three, the initial response to intra-arterial Priscoline was so favorable that conservative, nonsurgical management was continued. In nine patients the initial injection was accompanied by a paradoxic reduction in blood flow to the lower leg and foot which was demonstrated by a fall in skin temperature and development of cadaveric pallor of the injected extremity. Vasodilatation, as shown by redness, increased warmth and visible dilatation of the superficial veins occurred in the proximal portion of the extremity despite the changes in the distal areas. In most cases, vasodilatation of the distal portion of the extremity occurred after repeated injections.

A sustained paradoxic response of the type described above may be elicited by sympathectomy. If sufficiently protracted, it can cause gangrene of the already ischemic tissues and loss of the extremity. Reactions of this kind occurring in patients with extensive arterial occlusion following sympathectomy have been reported by Atlas, Freeman and others.[22, 23] Although the paradoxic response to intra-arterial Priscoline was evoked repeatedly during the early phase of treatment of these patients, in no instance was it sustained for a period long enough to produce complete devitalization of the distal tissues. Priscoline administration appears to be of value, there-

fore, in unmasking the "paradoxic response" in patients for whom sympathectomy is contemplated and in whom it would increase already existing damage.

Although gangrene occurred in seven extremities in this group of 12 patients, only two digits and one forefoot required amputation; all other gangrenous areas healed under treatment. Maintenance of adequate anticoagulant therapy caused no significant problems during the course of repeated arterial injections.

Discussion

Priscoline has now been in use for the treatment of peripheral vascular disease for many years. Numerous reports have confirmed the observations that the drug is an effective vasodilating agent. Its use, as well as the use of other presently available vasodilating agents is, however, definitely limited. Priscoline is effective orally, intravenously, or intra-arterially, but even when given by the latter route does not increase blood flow or prevent vasoconstriction following exposure to cold to as great a degree as some of the newer autonomic blocking agents (Dibenzyline and hexamethonium).[21]

Blood flow, as measured by skin temperature and plethysmographic studies, does not necessarily correlate, however, with clinical results. This may be due to the fact that these measurements reflect total blood flow which includes arteriovenous shunt flow, plus so-called "nutritional blood flow." "Shunt flow" may increase to a great degree in patients with organic vascular disease while nutritional flow is not greatly increased. Consequently, measurements may show an excellent increase in blood flow while little or no improvement occurs clinically. The converse may also be true; only a slight rise in skin temperature or blood flow may occur while a marked clinical improvement results. Therefore, it would appear that flow measurements by the presently available means do not always accurately predict the expected clinical results of any therapy.

There is some evidence to suggest that tolerance to drug effect develops after a prolonged period of therapy regardless of the drug used. For this reason, the long-term management of peripheral vascular disease with presently available drugs is not always satisfactory. The results are encouraging, however, in some cases where an increase in vasoconstrictor tone is present; namely, acrocyanosis, Raynaud's disease, and thromboangiitis obliterans. In causalgic states or in patients with ischemic pain excellent results have also been achieved.

Studies with Priscoline given by the intra-arterial route have indicated that this method of administration often produces better results than when the drug is used orally or intravenously. Side effects and reactions are minimal even in the older age groups.

Results indicate that intra-arterial Priscoline is often effective in the treatment of ulcerations or delayed wound healing secondary to diseases with increased vasoconstrictor tone and Raynaud's disease. Relief in various "causalgic" and pain states is also obtained. Treatment of these entities with hexamethonium and/or Dibenzyline is, however, quite satisfactory and, in many instances, the results are better with the latter drugs.[21] The use of these agents by conventional methods will relieve the physician of the necessity of using intra-arterial therapy with Priscoline. In the occasional case where a marked reaction to hexamethonium or Dibenzyline occurs, or in instances where these drugs are not available, or the physician is not acquainted with their action, intra-arterial Priscoline should be used.

Priscoline has proved to be most effective in providing relief of ischemic rest pain in patients with organic arterial disease. There is evidence of an increased "local" effect and the occasionally serious side effects noted after the use of other "general" blocking agents are rarely noted after intra-arterial Priscoline. This consideration is especially important when one considers that most patients with organic vascular disease are treated in a semi-Fowler's (foot down) position. If drugs such as hexamethonium, which produce marked postural hypotension, are used in these patients, there is a real danger of syncope and cerebral anoxia. If hypotension occurs and the patient must be placed in the head down position to prevent serious cerebral difficulties, the ischemic extremity is rendered more ischemic by being elevated. For this reason intra-arterial Pris-

coline, which does not produce marked blood pressure changes, is to be preferred in the treatment of these patients. Rest pain is often dramatically relieved and gangrenous areas healed rapidly. Exercise tolerance is, however, rarely increased.

Summary

1. Priscoline may be given intra-arterially (50 to 75 mg.) with safety and without difficulty. Untoward reactions are not common even in the older age group. A significant degree of "trapping" in the injected extremity is possible.

2. Intra-arterial administration is often effective in patients who have not responded to oral Priscoline.

3. Even when utilized intra-arterially, Priscoline does not often produce maximal release of vasomotor tone. The degree of vasodilatation is, however, often adequate for a clinical effect.

4. Results in 250 patients treated and studied with intra-arterial Priscoline indicate that the drug is most useful in the treatment of ischemic rest pain secondary to organic vascular disease. Increase in exercise tolerance or relief of "claudication" pain is not to be expected.

5. Intra-arterial Priscoline is effective in some cases of causalgia and delayed wound healing and in the treatment of ulcerations in Raynaud's disease. There is, however, little actual indication for the use of this agent in these entities. Other agents produce comparable or better results without the need for arterial punctures.

6. Drug therapy of peripheral vascular disease is not completely satisfactory even though potent agents are now available. Intra-arterial Priscoline may be used along with other drugs such as Dibenzyline and hexamethonium, but uniformly good results should not be expected.

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Sumario Español

La Priscolina se puede administrar intra-arterialmente sin dificultad. Reacciones no deseables ocurren infrecuentemente aún en pacientes de avanzada edad. La administración intra-arterial fué frequentemente efectiva en pacientes que no respondieron a la administración oral de la Priscolina. Aunque vasodilatación máxima no se obtuvo mediante la administración de Priscolina intra-arterial, el grado de vaso-dilatación obtenida es frecuentemente adecuado en cuanto al efecto clínico. Resultados en 250 pacientes indican que la Priscolina intra-arterial es de mayor beneficio en el tratamiento de dolor isquémico durante el descanso producido por enfermedad vascular oclusiva. Mejoría a la tolerancia al ejercicio fué infrecuente. Causalgia, cicatrización tardía y ulceración en la enfermedad de Reynaud's respondieron favorablemente en algunos casos.

REFERENCES

[1] Johnson, R. L., Freis, E. D., and Schnaper, H. W.: Hemodynamic changes in the small vessels in man as analysed by digital plethysmography. Angiology **2:** 412, 1951.

[2] Moser, M., Prandoni, A. G., and Mattingly, T. W.: Comparative effects of autonomic blocking agents on blood flow and vasomotor responses in vascular disease. To be published.

[3] Weissenbach, R. J., and Fanlong, L.: Resultats de l'injection intrarterielle du chlorhydrate de 2-benzyl-imidazoline. Rev. du rhum. **13:** 55, 1946.

[4] Kappert, A.: Untersuchungen uber intra arterielle therapie. Helvet. med. acta. **14:** 533, 1947.

[5] —: Zur behandlung mit intra-arteriellen injectionen. Helvet. med. acta **15:** 25, 1948.

[6] Alpert, S.: Discussion of Searles, P. W., and Nowill, W. K.: Cerebral vascular accidents; treatment by stellate ganglion blocks. South. M. J. **43:** 229, 1950.

[7] Lynn, R. B.: Effects of Priscoline on the peripheral circulation. Lancet **2:** 976, 1950.

[8] Wilson, J. L., and Quash, E. T.: Intra-arterial and oral Priscoline. Am. J. Surg. **81:** 336, 1951.

[9] Flasher, J., Van Scoyac, R. H., Mahoney, D. V., and Griffith, G. C.: Priscoline, skin

temperature and electrocardiographic study. Angiology **2:** 199, 1951.

[10] LIPPMAN, H. I.: Intraarterial Priscoline therapy for peripheral vascular disturbances. Angiology **3:** 69, 1952.

[11] MEIER, R., AND MUELLER, R.: Vascular effects of a new imidazoline derivative. Schweiz. med. wchnschr. **69:** 1271, 1939.

[12] AHLQUIST, R. P., AND WOODBURY, R. A.: The influence of benzylimidazoline (Priscol) in sympathomimetic vasoconstrictors and vasodilators. Federation Proc. **5:** 161, 1946.

[13] YONKMAN, F. F., AND CHESS, D.: Adrenolytic and sympatholytic actions of Priscol (benzylimidazoline). Proc. Soc. Exper. Biol. & Med. **61:** 127, 1946.

[14] AHLQUIST, R. P., HUGGINS, R. A., AND WOODBURY, R. A.: The pharmacology of benzylimidazoline (Priscol). J. Pharmacol. & Exper. Therap. **89:** 271, 1947.

[15] GRIMSON, K. S., REARDON, M. J., MARZONI, F. A., AND HENDRIX, J. P.: The effects of Priscol (2-benzyl-4,5-imidazoline HCl) on peripheral vascular diseases, hypertension and circulation in patients. Ann. Surg. **127:** 968, 1948.

[16] MEIER, R., AND MEYER, R.: On the peripheral point of attack of Priscol on the vascular system. Schweiz. med. wchnschr. **71:** 1206, 1941.

[17] HERMANN, J., JOURDON, F., AND BONNET, V.: Sympathicolytic action and adrenalin inversion with 2-benzyl-imidazoline, Compt. rend. Soc. biol. **135:** 1653, 1941.

[18] BAUEREISEN, B.: Circulatory effects of the benzylimidazoline: Priscol. Arch. Exper. Path. **199:** 161, 1942.

[19] CHESS, D., AND YONKMAN, F. F.: A new adrenolytic agent, 2-benzyl-imidazoline (Priscol). Federation Proc. **4:** 114, 1945.

[20] MOSER, M., AND FOWLER, F.: The treatment of causalgia and related pain states with autonomic blocking agents. To be published.

[21] —, PRANDONI, A. G., ORBISON, J. A., AND MATTINGLY, T. W.: Clinical experience with sympathetic blocking agents in peripheral vascular disease. Ann. Int. Med. **38:** 1245, 1953.

[22] ATLAS, L. N.: Lumbar sympathectomy in the treatment of peripheral arteriosclerotic disease. Am. Heart J. **23:** 493, 1942.

[23] FREEMAN, N. E., LEEDS, F. N., AND GARDNER, G. E.: Sympathectomy for obliterative arterial disease; indications and contraindications. Ann. Surg. **126:** 873, 1947.

Dibucaine Hydrochloride in the Control of K-Strophanthoside-Induced Ventricular Tachycardia and Other Toxic Manifestations

By A. Sidney Harris, Ph.D., Abdo Bisteni, M.D., George A. Pettit, B.S., and Calvin W. Hoffpauir, B.S.

Dibucaine hydrochloride in relatively small doses terminated high frequency ventricular tachycardia induced by toxic doses of K-strophanthoside in 9 of 10 dogs. Dibucaine was antidotal to glycoside-induced vagotonia and improved the alertness and apparent general condition of the animals that received it. One death occurred in the 10 strophanthoside tachycardia animals treated with dibucaine, a mortality rate of 10 per cent. Four deaths occurred in seven dogs that received similar doses of strophanthoside but no dibucaine, a mortality rate of 57 per cent.

DIBUCAINE HYDROCHLORIDE* has been found in a previous study[1] to be an effective suppressor of ventricular tachycardia resulting from myocardial infarction in dogs. This effect was increased and toxic reactions to dibucaine were prevented or minimized by prior administration of phenobarbital. Ventricular tachycardia that results from myocardial infarction is a difficult arrhythmia to control, providing a severe test for antiectopic-rhythm drugs. Results with dibucaine and phenobarbital in those tests suggested that dibucaine might be an effective agent for the suppression of ectopic cardiac rhythms resulting from other causes.

The following experiments were designed to test the effects of dibucaine upon ventricular tachycardia that results from toxic overdosage with digitalis glycosides. It was found that the antidotal effects were not confined to the suppression of ectopic impulses but extended also to certain other aspects of toxic reactions to K-strophanthoside and lanatoside C†. Strophanthoside was chosen as the principal glycoside for use in the study.

Technics

A standard dose of strophanthoside for inducing ventricular tachycardia was established in a preliminary series of experiments. It was found that 0.1 mg. per kilogram sufficed to produce ventricular tachycardia in almost all animals. Smaller doses did not produce the tachycardia. The strophanthoside was administered in a single intravenous dose.

Following these preliminary experiments, 19 dogs were used. Seven were used for tests to record the duration of the strophanthoside-induced ventricular tachycardia when not treated. Ten dogs were used in tests of the ectopic impulse suppressor effect of dibucaine in strophanthoside tachycardia. Two dogs were used to answer specifically the question whether or not dibucaine antagonizes the bradycardia that results from vagotonia induced by cardiac glycosides (strophanthoside was used in one of these animals and lanatoside C in the other).

Morphine, 5 mg. per kilogram, was administered 30 minutes prior to strophanthoside in all dogs except two which received barbiturates. The purpose of the morphine and the barbiturates was the prevention of the severe retching and vomiting which otherwise would be produced by strophanthoside.

In the experiments to test the effectiveness of

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* The dibucaine hydrochloride (Nupercaine hydrochloride) used in these experiments was supplied by Ciba Pharmaceutical Products, Inc. The shortened name dibucaine is used throughout the remainder of this paper.

† The K-strophanthoside (Strophosid) and lanatoside C (Cedilanid) used in this study were supplied by Sandoz Chemical Works, Inc. The names strophanthoside and lanatoside C are used in the remainder of the paper.

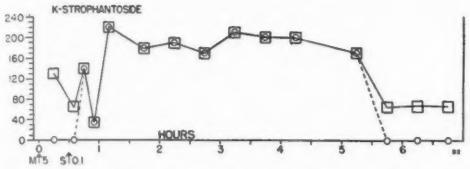


FIG. 1. Chart of strophanthoside-induced ventricular tachycardia without dibucaine treatment. M5, morphine, 5 mg. per kilogram, subcutaneously. S 0.1, strophanthoside 0.1 mg. per kilogram. Squares = heart rate. Circles = ectopic rate.

The latency of onset of tachycardia after injection varied between 3 and 27 minutes, the average being about 11 minutes. A chart of one of the tachycardias without dibucaine treatment is shown in figure 1.

The durations and maximal frequencies of the strophanthoside ventricular tachycardias in seven dogs that were not treated with dibucaine are shown in table 1. The maximal frequencies in the various experiments ranged

TABLE 1.—*Effects of Strophanthoside without Dibucaine*

Exp. no.	Dose stroph. *mg./Kg.*	Ventricular tachycardia		Commments
		Max. freq.	Duration after inj. stroph.	
S1	0.1	250	4 hr. 20 min.	Died 48 hours after injection.
S2	0.1	220	4 hr. 45 min.	Appeared very sick during experiment.
S3	0.1	210	5 hr. 15 min.	Appeared very sick during experiment.
S4	0.12*	210	6 hr. 30 min.	Died 4 hr. 55 min. after tachycardia was produced by additional 0.02 mg. per Kg.
S5	0.1	210	3 hr. 30 min.	Died 4 days after injection.
S6	0.1	210	Died 55 min.	Very sick, Cheyne-Stokes respiration. Died 55 min. after injection.
S7	0.1	260	1 hr. 30 min.	Appeared very sick.

Each animal received morphine sulfate, 5 mg. per Kg., to prevent retching and vomiting.

Duration is measured from time of injection to last record that showed ectopic activity.

* Injection of strophanthoside, 0.1 mg. per Kg., did not produce tachycardia in this animal. An additional 0.02 mg. per Kg., was given 1 hour 45 minutes after first injection. Tachycardia followed and persisted to within a few minutes of exitus by cardiac arrest.

dibucaine upon the ventricular tachycardia, the routine procedure was as follows. Morphine, 5 mg. per kilogram, subcutaneously was followed after an interval of 20 to 30 minutes by the intravenous injection of the standard dose of strophanthoside. After the tachycardia was fully established, as demonstrated by series of electrocardiograms, the intravenous infusion of dibucaine was begun. Dibucaine was administered in Locke's solution at a constant rate of 2 mg. per kilogram per hour. The concentration was 2 mg. of strophanthoside per kilogram of animal weight per 100 cc. Infusions were made from a burette via a polyethylene catheter in a saphenous vein.

RESULTS

Ventricular tachycardia was produced in 14 of 17 dogs by strophanthoside, 0.1 mg. per kilogram intravenously. In each of the three animals in which this dose failed to produce tachycardia, an additional dose of 0.02 mg. per kilogram precipitated the tachycardia.

from 210 to 260 per minute. Two dogs had tachycardia until death terminated the tests.

Spontaneous termination of the tachycardia occurred in the other five dogs after periods of one and one half hours to five and one quarter hours following injection of the standard tachycardia-inducing dose of strophanthoside. Four deaths occurred in the seven dogs that received tachycardia-inducing doses of strophanthoside but were not treated with dibucaine.

The infusion of dibucaine was begun in each of the 10 dibucaine-treated dogs soon after the tachycardia appeared to be leveling off at a high frequency, 190 to 265. Electrocardiograms reproduced in figure 2 show the ventricular tachycardia (250 per minute) that developed soon after the injection of strophanthoside, and the normal rhythm that was recorded during the first infusion of dibucaine

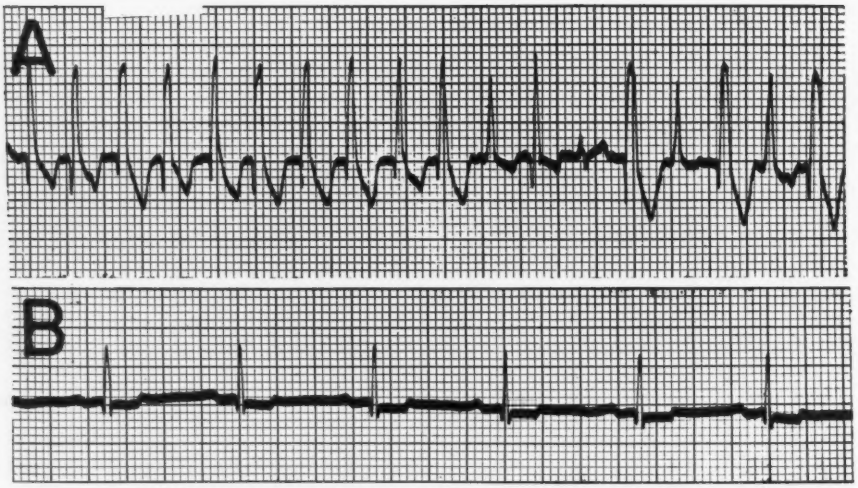


FIG. 2. (*A*) Electrocardiogram showing ventricular tachycardia, 250 per minute, 25 minutes after intravenous injection of strophanthoside, 0.1 mg. per kilogram. (*B*) Sinus rhythm, 85 per minute, after infusion of dibucaine (Nupercaine), 1.3 mg. per kilogram.

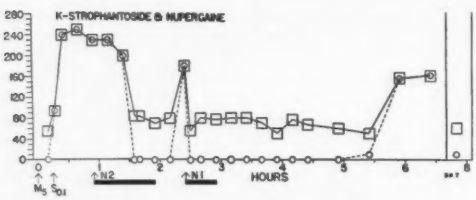


FIG. 3. Chart showing complete experiment from which figure 2 is taken. Squares = heart rate. Circles = ectopic rate.

in an illustrative experiment. The chart from the same experiment (fig. 3) shows the time course of the arrhythmia and treatment in detail. A normal rhythm was restored when the first infusion was about two thirds finished, that is, after administration of about 1.3 mg. per kilogram. The 2 mg. per kilogram infusion was completed and administration stopped. Thirty minutes after the first infusion was finished, ventricular tachycardia returned with a rate of 180 per minute. An additional infusion quickly restored normal rhythm. The infusion was continued until 1 mg. per kilogram had been administered. The rhythm remained normal for two and one half hours after this infusion and then ventricular tachycardia reappeared. Without further treatment the tachycardia subsided spontaneously within the following three hours.

Ventricular tachycardia was suppressed and normal rhythm restored by dibucaine before as much as 2 mg. per kilogram was infused in 9 of the 10 dogs. The other dog appeared very sick following strophanthoside and before dibucaine, and died in cardiac arrest just at the end of infusion of dibucaine, 2 mg. per kilogram in one hour. Administration of this quantity of dibucaine at the rate of infusion employed has been shown to be quite safe in a previous series of 22 dogs.[1] This fatality occurred in one of the two dogs in the treated group which had required an additional dose of strophanthoside (0.02 mg. per kilogram) to induce ventricular tachycardia. The data upon these 10 experiments are summarized in table 2.

Ventricular tachycardia returned after it had been stopped by dibucaine in four of the nine animals, and remained permanently stopped after the first infusion of dibucaine in the other five. An additional small infusion restored normal rhythm permanently or for a period of hours in each of the four animals with recurrence.

Sinus Bradycardia due to Morphine, and to Cardiac Glycoside. The morphine which was used for sedation and antiemetic effect produced a bradycardia which developed before

TABLE 2.—*Effects of Dibucaine in Antagonizing Toxic Reactions to Strophanthoside*

Exp. no.	Dose stroph. *mg./Kg.*	Dibucaine *mg./Kg.*	V. tachycardia		Comments
			Max. freq.	Time of suppres.*	
SN1	0.1	2	250	45 min.	Ectopic activity returned 15 min. after 1st suppression. Additional 1 mg./Kg. required.
SN3	0.1	3	220	45 min.	No recurrence of ectopic activity.
SN4	0.1	2	250	45 min.	No recurrence of ectopic activity.
SN5	0.1	3	265	45 min.	Slight return of ectopic activity within minutes after 1st cessation. Sharp increase to 170, 2 hr. 20 min. later. Additional infusion of dibucaine, 1 mg./Kg., restored normal rhythm when only half complete.
SN7	0.1	3	250	40 min.	Ectopic activity returned 50 min. after 1st suppression. Additional 1 mg./Kg. dibucaine restored normal rhythm. Ventricular tachycardia, rate 160 returned again 3 to 5 hr. after second suppression.
SN8	0.12	3	220	30 min.	No recurrence of ectopic activity.
SN9	0.1	4	240	1 hr.	Ectopic activity returned 1 hr. after 1st suppression. Additional 1 mg./Kg. administered to suppress. No further return.
SN10	0.1	2	220	15 min.	No recurrence of ectopic activity.
SN11	0.1	2	200	40 min.	No recurrence of ectopic activity.
SN12	0.12	2	180		Died in cardiac arrest 2 hr. 20 min. after additional dose of strophanthoside, at end of infusion of dibucaine 2 mg./Kg.

* The durations in this column are the elapsed times between the beginning of dibucaine infusion and complete elimination of ectopic complexes. Reduction of ectopic frequency was evident within 15 to 30 minutes after the beginning of dibucaine infusion in 8 of the 10 animals including 1 of the 2 that received the larger total dose of strophanthoside, 0.12 mg. per Kg.

the injection of strophanthoside. During the ventricular tachycardia that was produced by the strophanthoside, the sinus rate was not observable. After the restoration of sinus rhythm by dibucaine, however, bradycardia again was evident. Sinus bradycardia was observed both before and after the ventricular tachycardia in eight of the nine dogs that received morphine before the administration of strophanthoside. Dibucaine was effective in stopping the ventricular tachycardia, but it evidently did not antagonize the sinus bradycardia. Since bradycardia can be produced by morphine and also by cardiac glycoside, differentiating experiments were planned to determine whether or not dibucaine would antagonize glycoside bradycardia not complicated by morphine.

Bradycardia was produced by cardiac glycosides in two dogs that did not receive morphine. Strophanthoside, 0.08 mg. per kilogram (subthreshold for ventricular tachycardia), was used to produce bradycardia in one of these dogs, and lanatoside C in the same dosage was used to produce bradycardia in the other one. The first of these two dogs received a sedative dose of pentobarbital sodium, 20 mg. per kilogram, instead of morphine for sedation and for prevention of nausea and vomiting. This dose, however, proved to be insufficient to prevent emesis. Following the administration of strophanthoside, the sinus rate showed first an increase and then a decrease. During nausea and vomiting, the sinus rate increased from the control level of 95 to 100 to a maximum of 165. This maximum rate was recorded within 10 minutes after injection of the strophanthoside, and lasted one and one half hours after which vomiting ceased and the sinus rate declined to 60 which may be regarded as a relative bradycardia in this dog. Dibucaine by venous infusion at a rate of 3

mg. per kilogram per hour increased the heart rate to 103 (and produced vomiting) within 15 minutes. After this there was no further emesis. The dibucaine infusion continued until 3 mg. per kilogram had been given. The heart rate stabilized at about 110 to 115 and remained within this range throughout the two hours of observation after termination of the infusion.

The second dog received pentobarbital sodium, 25 mg. per kilogram, for sedation and antiemetic action. This dose proved to be sufficient to prevent vomiting. Lanatoside C, 0.08 mg. per kilogram, produced a pronounced bradycardia, reducing the heart rate from an average of 85 in control records to a low of 58 within 15 minutes following administration. After the rate had remained at 58 to 60 for 30 minutes, dibucaine infusion began. Within 15 minutes (after infusion of 0.75 mg. per kilogram) the rate had risen to 105. The infusion was continued until 1.5 mg. per kilogram of dibucaine had been given. The heart rate remained between 90 and 130 for about three hours after which the bradycardia returned to a profound degree, varying between 30 and 40 per minute in a series of records. Another infusion of dibucaine, 1.5 mg. per kilogram in 30 minutes, produced an increase in rate to a quite normal frequency of 88. The amount of dibucaine administered was as yet insufficient to maintain permanently a normal sinus rate, therefore a third infusion was begun after an interval of 30 minutes. A normal heart rate again was restored before the end of the infusion of an additional 1.5 mg. per kilogram.

From the foregoing observations on bradycardia, it can be concluded that dibucaine in relatively small quantities antagonizes the bradycardia that results from the administration of digitalis glycosides, but that it does not have a similar effect on bradycardia that results from the action of morphine.

Toxic Reactions and Mortality Rates. Following the administration of the tachycardia-inducing dose of strophanthoside, the dogs appeared very depressed, weak and sick, although morphine prevented signs of nausea. After infusion of dibucaine, 1 to 2 mg. per kilogram, a remarkable improvement in the apparent condition of the animals was observed. More spontaneous movements of tail, eyes and limbs occurred, the eyes seemed clearer and the impression of all observers was that the dogs were more comfortable.

The mortality figures appear to offer more definite evidence that dibucaine antagonizes some toxic effects of glycosides other than ventricular tachycardia. Four deaths occurred in seven dogs that received tachycardia-inducing doses of strophanthoside but no dibucaine. In addition to the two dogs that died during the period of tachycardia (55 minutes and 6½ hours after injection) two others died 48 hours and 4 days, respectively, after injection, long after the ventricular tachycardia had ceased spontaneously. Exitus resulted from some other toxic effect or effects of strophanthoside. Mortality rate in the group not treated with dibucaine was 57 per cent. One death occurred in 10 dogs that received tachycardia-inducing doses of strophanthoside and subsequent treatment with dibucaine, a mortality rate of 10 per cent.

Although the mortality percentages undoubtedly would be altered in a larger series, the observations indicate that dibucaine antagonizes a variety of toxic manifestations of the organism to strophanthoside.

Discussion

Dibucaine has proved to be an effective suppressor of high frequency ventricular tachycardia resulting from intoxication with strophanthoside. The dose of dibucaine required over a period of hours has been small, 2 or 3 mg. per kilogram. This is about one third of the dosage required to control severe ventricular tachycardias resulting from myocardial infarction, even with the aid of phenobarbital.[1]

Phenobarbital was not used in the strophanthoside tachycardia experiments. The morphine that was used to counteract the emetic effect of strophanthoside undoubtedly prevented any emetic reactions that might have resulted from dibucaine administration.

Dibucaine was effective as an antidote to the bradycardia-inducing effect of strophanthoside and of lanatoside C. It also reduced the

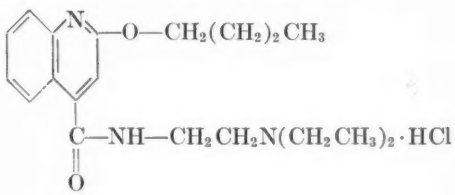
nortality rate and improved the condition of he animals as judged by appearance, attitude nd spontaneous movements. This series of lemonstrated antagonisms to manifestations of ardiac glycoside toxicity suggests strongly hat dibucaine has a general antidotal effect ipon toxic reactions to cardiac glycosides. A orollary suggestion is that dibucaine would enefit patients that have received overdosage f these substances, whatever the form of the oxic signs presented.

It is of interest that dibucaine does not ntagonize morphine-induced bradycardia. Since the vagus nerves are the effector pathways in both the morphine and glycoside bradycardias, it appears to follow that different nervous system components, afferent to the vagal nuclei, must act to produce the vagotonias that result from morphine and from cardiac glycosides, and that dibucaine blocks a component of the glycoside bradycardia path but no part of the morphine bradycardia mechanism. These findings may be regarded as evidence, though inconclusive, against the hypothesis that the principal toxic effects of cardiac glycosides in the heart muscle are secondarily produced by vagotonia.[2] In the present series of experiments, the appearance of the animals was improved and mortality was reduced although vagotonia (from morphine) persisted. It is probable that the principal toxic actions as well as the principal therapeutic actions of digitalis glycosides are produced by direct effects in cardiac muscle cells.

The salutary effects of dibucaine following toxic doses of strophanthoside are in marked contrast to the effects of procaine amide in animals that had received toxic doses of ouabain. Procaine amide evidently precipitated ventricular fibrillation and death in a significant number of animals.[3]

The finding that dibucaine in combination with phenobarbital is effective in the suppression of the ventricular tachycardia that results from myocardial infarction,[1] a difficult kind of tachycardia to control with the drugs most commonly used clinically,[4, 5] considered together with the good control by dibucaine of tachycardia produced by the glycoside suggests that dibucaine should be considered as an agent which might be useful in treatment of ventricular tachycardias from a variety of causes. It should be borne in mind that phenobarbital prevents undesirable reactions to dibucaine as well as to cocaine and other members of the cocaine-like local anesthetic series.[6, 7, 8, 9]

Interest in dibucaine as an agent for use in the treatment of ectopic rhythms is increased by reason of its chemical relationship to both quinidine and procaine. Dibucaine has been described chemically[10] as 2 butoxy-N-(2-diethylaminoethyl) cinchoninamide hydrochloride, with the structural formula:



Summary

K-strophanthoside, 0.1 mg. per kilogram, induced high frequency ventricular tachycardia in 14 of 17 dogs. In each of the other three animals an additional dose of 0.02 mg. per kilogram precipitated the tachycardia. Nausea and vomiting due to strophanthoside were prevented by a prior dose of morphine.

Ten dogs with strophanthoside-induced ventricular tachycardia were treated by intravenous infusion of dibucaine in Locke's solution. In 9 of the 10 dogs, the tachycardia was converted to sinus rhythm after infusion of less than 2 mg. per kilogram of dibucaine. Recurrences of the tachycardia in four of the nine animals were terminated promptly by small additional infusions.

Following strophanthoside, the dogs appeared weak and sick. Four deaths occurred among the seven dogs that did not receive dibucaine treatment, a mortality rate of 57 per cent. One death occurred in the 10 dogs that were subsequently treated with dibucaine, a mortality rate of 10 per cent. Improvement in apparent condition of the animals was noted soon after infusion of dibucaine began.

Dibucaine also antagonizes glycoside-in-

duced vagotonia, but does not antagonize morphine-induced vagotonia.

A variety of toxic manifestations of digitalis evidently are counteracted by dibucaine.

Sumario Español

Clorhidrato de dibucaine en cantidades relativamente pequeñas terminó taquicardias ventriculares de alta frequencia inducidas por dosis tóxicas de K-estrofantosido en 9 de 10 perros. Dibucaine fué antídoto para las vagotonias inducidas por glicósido y mejoró la viveza y la condición general de los animales a que se le administró. Una muerte ocurrió en las 10 taquicardias de estrofantosido tratadas con dibucaine: promedio de muerte, 10 por ciento. Cuatro muertes ocurrieron en siete perros que recibieron similares dosis de estrofantosido pero no dibucaine: promedio de muerte, 57 por ciento.

REFERENCES

[1] Bisteni, A., and Harris, A. S.: Effectiveness of Nupercaine hydrochloride and phenobarbital sodium in the suppression of ventricular tachycardia associated with acute myocardial infarction. Circulation **1:** 523, 1953.

[2] Kyser, F. A., Ginsberg, H., and Gilbert, N. C.: The effect of certain drugs upon the cardiotoxic lesions of digitalis in the dog. Am. Heart J. **31:** 450, 1946.

[3] Zapata-Diaz, J., Cabrera, E., and Mendez, R.: Acción de la procainamida (Pronestyl) sobre el corazon. II. Estudio experimental de los efectos de la asociacion digital procainamida. Arch. Inst. cardiol. México **21:** 644, 1951.

[4] Harris, A. S., Estandía, A., Ford, T. J., Jr., and Tillotson, R. F.: Quinidine lactate and gluconate in the suppression of ectopic ventricular tachycardia accompanying acute myocardial infarction. Circulation **4:** 522, 1951.

[5] —, Estandía, A., Ford, T. J., Jr., Smith, H. T., Olsen, R. W., and Tillotson, R. F.: The effects of intravenous procaine and procaine amide (Pronestyl) upon ectopic ventricular tachycardia accompanying acute myocardial infarction. Circulation **5:** 551, 1952.

[6] Tatum, A. L., Atkinson, A. J., and Collins, K. H.: Acute cocaine poisoning. Preliminary report of an experimental study. J.A.M.A. **84:** 1177, 1925.

[7] —, Atkinson, A. J., and Collins, K. H.: Acute cocaine poisoning, its prophylaxis and treatment in laboratory animals. J. Pharmacol. & Exper. Therap. **26:** 325, 1925.

[8] —, and Collins, K. H.: Acute cocaine poisoning and its treatment in monkeys (Macacus rhesus). Arch. Int. Med. **38:** 405, 1926.

[9] Knoefel, P. K., Herwick, R. P., and Loevenhart, A. S.: The prevention of acute intoxication from local anesthetics. J. Pharmacol. & Exper. Therap. **39:** 397, 1930.

[10] New and Nonofficial Remedies: American Medical Association, 1952. p. 31.

The Effect of Hypocapnia on Arterial Blood Pressure

By J. F. BURNUM, M.D., J. B. HICKAM, M.D., AND H. D. MCINTOSH, M.D.

In man, hypocapnia induced by hyperventilation causes a drop in arterial pressure. The calculated peripheral resistance is decreased, indicating a net vasodilatation. The forearm blood flow is markedly increased, and the vascular resistance of the forearm is much reduced. Persons with impaired function of the sympathetic nervous system continue to show these effects. The increase in forearm flow is not prevented by brachial block. These results suggest that hypocapnia acts directly on blood vessels to produce a net over-all vasodilatation and fall in blood pressure, and that this effect is not mediated through the nervous system, as usually supposed.

BREATHING carbon dioxide raises the blood pressure and hyperventilation lowers it in man and experimental animals. Changes in blood carbon dioxide are supposed to affect vessels both directly and by way of the vasomotor centers.[1] These actions are thought to be opposite in direction, with the central effect being the stronger. That is, a high carbon dioxide level causes an over-all vasoconstriction because of its effect on the vasomotor centers, even though the direct action is to dilate vessels. Loss of carbon dioxide has opposite effects, both centrally and locally. These conclusions are based on animal experiments.

It is the purpose of this paper to describe the effects on vascular tone of lowering carbon dioxide by hyperventilation in (1) normal subjects and (2) patients in whom portions of the nervous system have been destroyed by disease or surgery or blocked by drugs. The results of this study do not support the conventional concept of the means by which carbon dioxide affects vascular tone.

METHODS

Hyperventilation studies, unless otherwise specified, were conducted on recumbent subjects during one-minute periods of maximal voluntary forced breathing of either room air or a 5 per cent carbon dioxide, 21 per cent oxygen gas mixture. Procedures included simultaneous measurements of forearm blood flow by plethysmography, intraarterial pressure, pulse rate, cardiac output by dye dilution method[2] and arterial blood pH and carbon dioxide content;[3, 4] from the latter blood carbon dioxide tension was calculated. Local forearm vascular resistance was calculated as

$$\frac{\textit{mean blood pressure (mm. Hg)}}{\textit{forearm blood flow (cc./min./100 cc. tissue)}}$$

and over-all peripheral resistance as

$$\frac{\textit{mean blood pressure (mm. Hg)}}{\textit{cardiac output (L/min.)}}$$

Forearm blood flows at 37 C. with hand excluded,[5] central venous pressure and intra-arterial pressures were measured with the use of strain gauges and a Sanborn Poly-Viso oscillograph. Single determinations of cardiac output were separated by 15-minute intervals, and the Evans blue dye was injected through a standard cardiac catheter threaded into one of the intrathoracic great veins (subclavian or superior vena cava) or right atrium. Arterial blood samples for dye analysis were collected from the brachial or femoral artery.

Brachial plexus block was achieved by infiltration with 20 cc. of 2 per cent xylocaine containing 1:300,000 epinephrine.*

RESULTS

Control Subjects

After a period of one minute of forced breathing, the arterial blood carbon dioxide tension was commonly halved, falling to around 20 mm. Hg, and the pH rose to around 7.6. Maximal forced voluntary hyperventila-

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Dr. Burnum was formerly a Life Insurance Medical Research Fellow.

Dr. McIntosh is a Research Fellow of the American Heart Association.

* Courtesy of Dr. W. K. Nowill, Department of Anesthesiology, Duke University School of Medicine.

TABLE 1.—*Circulatory Changes during Hyperventilation (Air). Control Subjects*

Case no.	State	Mean B.P. *mm. Hg*	Pulse rate, per. min.	Cardiac output, *L./min.*	Forearm blood flow, *cc./min./ 100 cc. arm*	Vascular resistance		Mean cir. time, *sec.*	pH 37°	pCO_2, *mm. Hg*
						Over-all Periph-eral, *Mean BP/ Cardiac Output*	Forearm, *Mean BP/ Forearm flow*			
1	Rest	56	68	8.0	12.2	7.0	4.6	15.4	7.39	
	Hyperventilation	31	114	18.7	31.0	1.7	1.9	6.9	7.55	
2	Rest	89	64	7.2	7.5	12.3	11.9	19.2	7.38	40.0
	Hyperventilation	63	125	8.1	20.0	7.8	3.8	10.5	7.64	16.8
3	Rest	85	82	8.9	6.4	9.5	13.3	14.1	7.45	35.5
	Hyperventilation	63	160	10.1	8.4	6.2	10.0	8.0	7.62	19.3
4	Rest	81	76	7.6	11.0	10.7	7.2	14.5	7.39	44.8
	Hyperventilation	63	124	10.0	27.3	6.3	2.7	9.3	7.60	22.4
5	Rest	91	70	6.6	9.7	13.8	9.4	21.1	7.35	45.1
	Hyperventilation	70	130	6.8	19.3	10.3	5.4	11.7	7.59	19.0
6	Rest	87	94	7.4	8.1	11.7	10.8	15.3		
	Hyperventilation	53	160	13.9	20.5	3.8	2.8	8.4		
7	Rest	99	68	7.9	11.2	12.5	8.8	24.0	7.38	47.0
	Hyperventilation	75	104	10.4	35.2	7.2	3.0	13.6	7.56	27.0
8	Rest	93	80	4.4		21.1		15.5	7.39	40.0
	Hyperventilation	76	140	4.8		15.8		12.1	7.60	20.0
9*	Rest	137	90	5.3	8.3	25.8	16.5	16.5	7.35	41.4
	Hyperventilation	115	140	12.0	21.8	9.6	5.3	7.6	7.60	19.2

* Essential hypertension.

tion on 5 per cent carbon dioxide produced little or no change in the arterial blood carbon dioxide tension. When normal subjects are allowed to breathe 5 per cent carbon dioxide at will, there is an average increase of approximately 10 mm. Hg in the arterial carbon dioxide tension. Selected data from eight normal subjects and one hypertensive patient in whom the cardiac output was measured are presented in table 1. Figure 1 shows a schematic summary of the data pooled from all the control subjects.

Mean arterial pressure fell during the period of one-minute overbreathing in 33 of the 35 subjects and was unchanged in two. The average maximal fall was 18 mm. Hg. In some subjects this fall was transient, with recovery or even overshoot of the pressure during hyperventilation (fig. 2). In other instances recovery was delayed until after the cessation of the hyperventilation. In 16 patients forced overbreathing of a 5 per cent carbon dioxide mixture caused no change in pressure. Hyperventilation on air caused a striking increase in heart rate; on 5 per cent carbon dioxide only a moderate increase.

The cardiac output during hyperventilation on air was measured in nine subjects. It increased an average of 50 per cent. The circulation time was halved (average decrease 43 per cent). Measurements were made on three subjects hyperventilating on 5 per cent carbon dioxide; the output decreased in two of the three subjects and was unchanged in one.

Central venous pressure was measured in the right atrium or superior vena cava in seven subjects. There was no change in six and a rise of 5 mm. Hg in one.

In 16 subjects hyperventilation on air

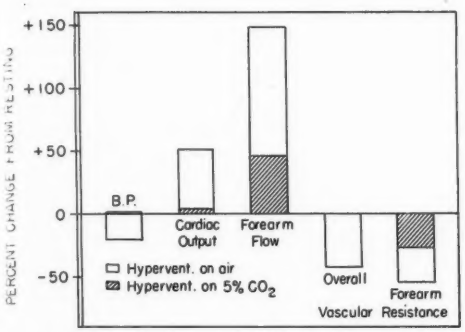

FIG. 1. Mean values of circulatory changes during recumbent hyperventilation in control subjects are presented as per cent change from resting measurements. During overbreathing on air the blood pressure falls and cardiac output and forearm blood flow rise; the calculated over-all and local forearm vascular resistance decrease. During hyperventilation on 5 per cent carbon dioxide there is only a small increase in forearm flow. These average changes were calculated from data on blood pressure in 35 subjects, forearm flow in 16 subjects, and cardiac output in 9 subjects.

increased the blood flow in the forearm to an average of 2.5 times the control level. Hyperventilation on 5 per cent carbon dioxide also increased the flow, but the increase averaged only a third as much as when hypocapnia was allowed to develop. This effect on forearm flow is similar to that recently reported by Clarke.[6]

Comment. In normal subjects overbreathing on air causes tachycardia, fall in arterial pressure, increased cardiac output and increased forearm blood flow. The increase in cardiac output in the presence of a reduced mean blood pressure indicates an over-all fall in peripheral resistance. The forearm is one of the areas where the resistance is lowered.

These data are in general agreement with those in the literature. Henderson[7] pointed out that Ewald in 1873 produced hypotension and apnea in dogs by hyperventilation, and Mosso found the same effects in man. The latter coined the word "acapnia" from the Greek *kapnos* meaning "smoke." Henderson showed that the fall in blood pressure in both

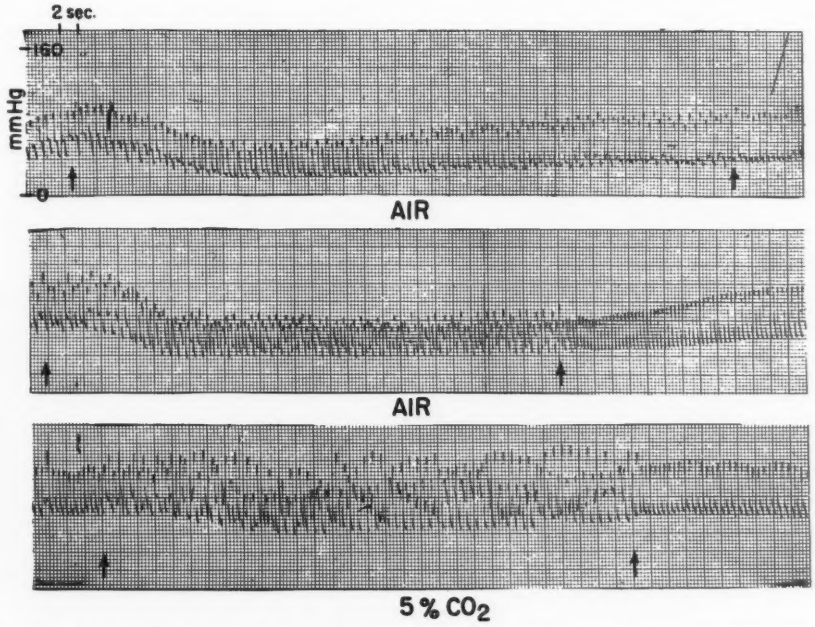

FIG. 2. Continuous intra-arterial pressure tracings during recumbent hyperventilation in normal subjects. During hyperventilation on air the arterial pressure falls but may tend to recover while overbreathing continues, top record, or not until later, middle record. On 5 per cent carbon dioxide no significant fall occurs. (Arrows indicate period of hyperventilation.)

dog and man was prevented by breathing a carbon dioxide mixture instead of air.

Roome[8] overventilated dogs in a Drinker respirator and demonstrated that the fall in arterial pressure resulted from over-all peripheral vasodilation and was prevented by breathing carbon dioxide. The cardiac output was measured by the direct Fick method.

Dale and Evans found in the cat that hyperventilation hypotension was largely prevented by overventilation on 5 per cent carbon dioxide and that acutely raising the pH with sodium bicarbonate to levels attained during hyperventilation on air did not cause a fall in pressure. They postulated that loss of carbon dioxide caused the fall in pressure and that this effect of low carbon dioxide was a central one since hyperventilation on air after destruction of the spinal cord caused a small rise in pressure, supposedly due to the now unveiled peripheral effects of hypocapnia.

Standard physiology texts have accepted Dale and Evans' explanation that lowering of the arterial carbon dioxide tension tends to cause vasoconstriction through local effect on vessels, but this effect is not demonstrable in the intact animal because of vasodilatation induced by the central effects of the low carbon dioxide tension. If this explanation is correct for man, one would expect the vasodilator effects of a low carbon dioxide tension to be lessened or absent in patients with a large portion of the vasomotor nerves destroyed by disease or blocked by suitable drugs. This hypothesis has been tested on appropriate patients.

Patients with Postural Hypotension

Observations were made on three subjects complaining of postural fainting. Two subjects had the classic syndrome of orthostatic hypotension with fixed pulse, impotence and impaired sweating as described in the classic paper of Bradbury and Eggleston.[10] The third patient was incapacitated 12 months after bilateral lumbar sympathectomy. The disturbances in reflex regulation were so marked that we believed she might have had poor postural regulation before operation. In each instance, at least partial paralysis of the vasomotor nerves was present. The Valsalva maneuver caused a major fall in arterial pressure and upon release of the strain, no overshoot in pressure occurred.

Hyperventilation on air in the recumbent position caused a large fall in arterial pressure with delayed recovery and no overshoot of pressure upon resumption of normal respiration (fig. 3). The cardiac output and forearm blood flow tended to increase, the circulation

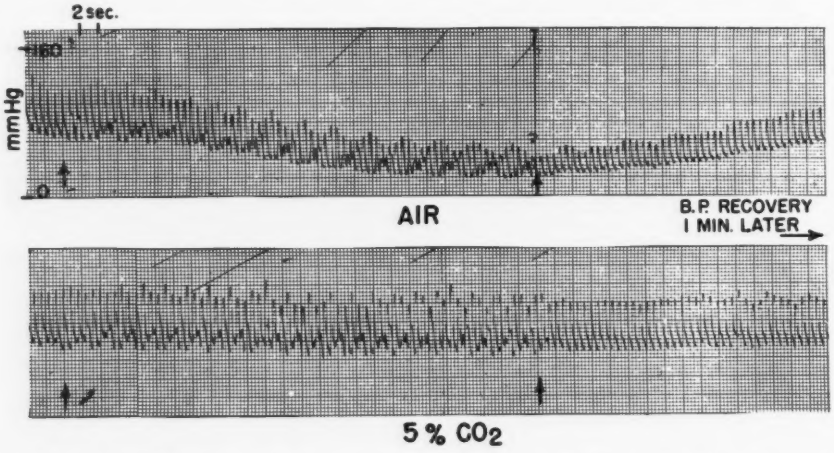

FIG. 3. Continuous intra-arterial pressure tracings in orthostatic hypotension during recumbent hyperventilation on air and 5 per cent carbon dioxide. A mean blood pressure fall of 60 mm. Hg occurs during overbreathing on air with a delayed recovery after resumption of normal respiration. No change occurs if hyperventilation is conducted on 5 per cent carbon dioxide. In both instances the pulse rate is fixed. (Arrows indicate period of hyperventilation.)

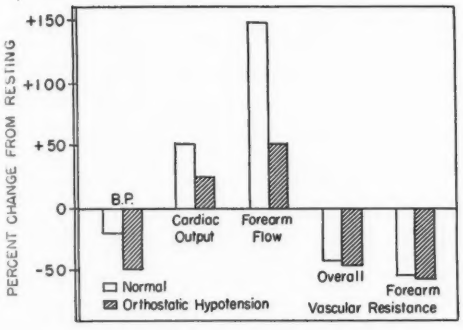

FIG. 4. Circulatory changes during recumbent hyperventilation on air in normal vs. orthostatic hypotension represented as mean per cent change from resting control values. In orthostatic hypotension the blood pressure fall is greater than normal but the fall in calculated resistance is about the same.

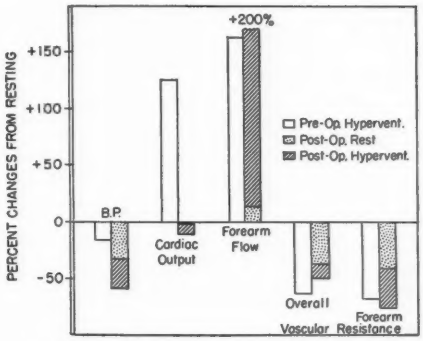

FIG. 5. Mean circulatory changes from the resting state during recumbent hyperventilation on air before and 7 weeks after sympathectomy. All changes are related to the preoperative resting values. After surgery there was a fall in resting arterial pressure and calculated vascular resistance with some increase in forearm blood flow. During hyperventilation there was an even greater proportional fall in pressure than occurred before operation, but vascular resistance fell to approximately the same level in both instances.

time to shorten and the calculated local forearm and over-all peripheral resistance to decrease. Figure 4 gives a graphic presentation of the data.

Hyperventilation on 5 per cent carbon dioxide largely prevented any circulatory changes.

Patients after Sympathectomy

Studies were done on one patient before and seven weeks after the second stage of a bilateral sympathectomy from T-1 to L-1 (fig. 5). All changes are related to the preoperative resting values. Removal of this large portion of the sympathetic chains did not change the over-all decrease in peripheral resistance and in forearm resistance produced by hyperventilation on air. Hyperventilation on 5 per cent carbon dioxide did not lower the pressure.

Observations were made on five patients who had had bilateral sympathectomy for hypertension from T-1 to L-1 from one to eight years previously and on one patient with essential hypertension with his vasomotor responses blocked by hexamethonium. In all cases, release of Valsalva maneuver caused no overshoot or bradycardia, indicating continued interruption of the visceral sympathetic pathways. Data from the control and sympathectomized groups are compared in figure 6. Measurements are averaged and presented as per cent changes during hyperventilation from resting values. The two groups are similar,

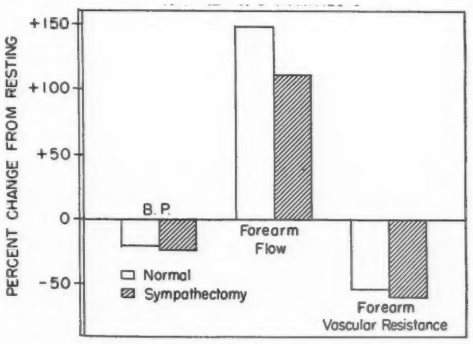

FIG. 6. Mean circulatory changes during recumbent hyperventilation on air in normal vs. sympathectomized patients presented as per cent change from resting values. Changes in sympathectomized patients generally resemble those in normal subjects.

except that the sympathectomized subjects showed no substantial recovery of arterial pressure during the course of hyperventilation, such as occurs in some normal subjects. No significant changes occurred when overbreathing a 5 per cent carbon dioxide mixture.

Subjects after Brachial Plexus Block

Brachial block was performed on one patient with an old hand injury, in whom the rest of the

extremity was normal, and on one normal subject. In each case the effectiveness of sympathetic block was indicated by the skin of the arm becoming hot, dry and flushed. The arm was anesthetized and almost totally paralyzed. In addition there was a Horner's syndrome and phrenic paralysis on the blocked side in one case. The data are summarized in table 2. In both cases before block, hyperventilation on air produced the usual fall in blood pressure, rise in forearm blood flow and fall in forearm resistance. After block the resting forearm flow increased, but not to the extent of that produced by preblock hyperventilation. After block, during overbreathing the blood pressure fell as usual, and the forearm flow increased and the local resistance fell to precisely the same levels reached before block.

TABLE 2.—*Effect of Brachial Plexus Block*

Subject	State	Mean BP, *mm. Hg*	Forearm blood flow, *cc./min. 100 cc. arm*	Forearm resistance, *Mean BP/ forearm flow*
A	Control			
	Rest	101	6.5	15.6
	Hypervent.	80	23.4	3.4
	Block			
	Rest	107	16.5	6.5
	Hypervent.	93	24.8	3.7
B	Control			
	Rest	86	6.3	13.7
	Hypervent.	76	20.0	3.6
	Block			
	Rest	89	13.2	6.7
	Hypervent.	82	22.0	3.7

COMMENT

These data indicate that in man a loss of carbon dioxide from overbreathing has an over-all vasodilating effect. In normal subjects the fall in pressure is restricted by a combination of an increase in cardiac output and the expected effect of vasoconstriction in various areas secondary to the fall in arterial pressure. These are the familiar homeostatic adjustments which keep the arterial pressure at its surprisingly constant level. The importance of these adjustments for regulating the arterial pressure is well shown in the patients with symptoms of postural hypotension and in the patient with the recent extensive sympathectomy, who had greater and more prolonged falls in pressure during hyperventilation than did the normal subjects. The fact that a fall in carbon dioxide tension causes a marked fall in peripheral resistance in patients with destruction of a large portion of the autonomic nervous system argues against a central effect and suggests that lowering carbon dioxide tension causes vasodilatation because of a direct effect on certain vessels. Brachial blocks established the fact that at least in the forearm a lowering of carbon dioxide tension caused vasodilation by local action.

These data are not to be interpreted as meaning that lowering of the arterial carbon dioxide tension causes vasodilatation in all organs. It is well known that in the cerebral vessels where vasomotor activity is low, acapnia causes a rise in resistance. It does appear that the sum of all the changes in resistance add up to vasodilation and that if the nervous system is not working properly this vasodilation is sufficient to cause a marked fall in arterial blood pressure.

Neither do these data shed any light on the effects of high carbon dioxide tension on the blood vessels. The fact that a low carbon dioxide tension causes a fall in peripheral resistance does not mean that sufficiently high carbon dioxide tension might not have the same effect. For example, both too much potassium and too little potassium cause paralysis.

These data are convincing evidence that the role of carbon dioxide tension in arterial pressure homeostasis needs further investigation.

SUMMARY AND CONCLUSIONS

1. Hypocapnia, induced by voluntary hyperventilation, causes a substantial decrease in the peripheral vascular resistance and blood pressure of normal subjects, and a substantial increase in forearm blood flow.

2. These effects of hypocapnia persist in subjects who have extensive loss of function of the sympathetic nervous system, resulting from disease, surgery, or the use of autonomic blocking drugs.

3. Brachial block does not substantially

hange the response to hypocapnia of forearm ascular resistance and forearm blood flow.

4. It is probable that vasodilatation produced by hypocapnia in man is the net result of direct action on the vessels in different ascular areas and is not mediated by the nervous system.

Sumario Español

En el hombre la hipocapnia inducida por la hiperventilación causa un decremento en presión arterial. La resistencia periférica calculada esta disminuida, indicando una vasodilatación neta. La circulación del antebrazo es marcadamente aumentada, y la resistencia vascular muy reducida. Personas con función deteriorada del sistema simpático continuan demostrando estos efectos. El aumento en circulación del antebrazo no se evita por medio de un bloqueo braquial. Estos resultados sugieren que la hipocapnia actua directamente en los vasos para producir una vasodilatación neta y un decremento en presión arterial, y que este efecto no es mediado por el sistema nervioso como se había supuesto.

REFERENCES

[1] Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 5. Baltimore, Williams & Wilkins, 1950.

[2] Hamilton, W. F., Moore, J. W., Kinsman, V. M., and Spurling, R. G.: Studies in circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. Am. J. Physiol. **99:** 534, 1931, 1932.

[3] Peters, J. P., and van Slyke, D. D.: Quantitative Clinical Chemistry. Vol. II. Methods. Baltimore, Williams & Wilkins, 1932.

[4] Van Slyke, D. D., and Sendroy, J., Jr.: Studies of gas and electrolyte equilibria in blood. XV. Line charts for graphic calculations by the Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. J. Biol. Chem. **79:** 781, 1928.

[5] Grant, R. T., and Bruce Pearson, R. S.: The blood circulation in the human limb; observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. Clin. Sc. **3:** 119, 1938.

[6] Clarke, R. S. J.: The effect of voluntary overbreathing on the blood flow through the human forearm. J. Physiol. **118:** 537, 1952.

[7] Henderson, Y.: Acapnia and shock. I. Carbon dioxide as a factor in the regulation of the heart rate. Am. J. Physiol. **21:** 126, 1908.

[8] Roome, N. W.: The cardiac output in hyperventilation by external alternating pressure. Am. J. Physiol. **104:** 142, 1933.

[9] Dale, H. H., and Evans, C. L.: Effects on the circulation of changes in the carbon dioxide content of the blood. J. Physiol. **56:** 125, 1922.

[10] Bradbury, S., and Eggleston, C.: Postural hypotension; a report of three cases. Am. Heart. J. **1:** 73, 1925.

Quantitative Studies in Man of the Cardiovascular Effects of Reflex Vagal Stimulation Produced by Carotid Sinus Pressure

II. Rates of Impulse Formation of Two Cardiac Pacemakers in Each of Three Individuals

By ARTHUR J. LINENTHAL, M.D., WITH THE TECHNICAL ASSISTANCE OF LEE CAPLITZ, B.S.

In each of three individuals, carotid sinus pressure produced a shift of the control of the heart beat from the dominant pacemaker to an ectopic, slower or faster, site of impulse formation. In each instance, it was possible to measure the fundamental rates of the two practically simultaneous pacemakers over fairly wide ranges of variation in rate. A direct, linear relationship was found to exist.

A GREAT deal of clinical information is available regarding the effect of numerous specific factors (for example, nervous stimulation and blood gas and electrolyte changes) on the rates of impulse formation in individual cardiac pacemakers. However, there are but few observations in the same person on the relative changes in the rates of two simultaneously-active pacemakers. The simultaneous rates of impulse formation in the sinoatrial node and in an ectopic ventricular focus in the same individual have occasionally been measured repeatedly.[1, 2, 3] In any one patient, however, the data are not sufficient for a precise comparison of changes in the fundamental rates of the two pacemakers as a result of spontaneous variations.

In each of three patients with coronary artery disease and a sensitive carotid sinus cardiac reflex, during repeated electrocardiographic observations of the effects of carotid sinus pressure it was possible to measure the fundamental rates of impulse formation in two practically simultaneous cardiac pacemakers. In each case, the two rates could be determined over fairly wide ranges of spontaneous variation. A direct, linear relationship was found to exist in each patient between varying rates of the two pacemakers: the sinoatrial node and a slower atrioventricular nodal pacemaker; the sinoatrial node and a faster atrioventricular nodal pacemaker; and the atrioventricular node and a slower ventricular pacemaker.

The presentation and analysis of our observations in these patients form the basis of the present report.

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PATIENTS

N. S. (BIH no. 17498), a 70 year old man, had had typical attacks of angina pectoris for at least 10 years. He was ambulatory throughout the three year period during which our observations were made. With the exception of occasional blood pressure elevations (to 190/90) there were no significant cardiovascular findings. Except for left axis deviation and the shifts in pacemaker described below, his electrocardiograms were always within normal limits. On 19 different days during a three-year period the cardiac effects of 101 applications of carotid sinus pressure were observed, 58 on the right and 43 on the left. Certain data in this patient have already been reported[4] and other data are to be presented elsewhere.[5]

M. S. (BIH no. M15069) was a 75 year old man with benign prostatic hypertrophy who was treated by two-stage suprapubic prostatectomy. In the past he had had frequent attacks of angina pectoris, but none had occurred within the previous year.

There was no evidence of congestive heart failure. His blood pressure was sometimes slightly elevated (to 170/100) and a chest plate showed very slight cardiac enlargement to the left. With the exception of the shifting pacemaker to be described below, his electrocardiograms showed only left axis deviation and left ventricular hypertrophy. On 31 days during a two-month period of hospitalization the electrocardiographic effects of 184 applications of carotid sinus pressure were observed, 178 on the left and 6 on the right. Numerous long control electrocardiograms were also recorded on most of these days. In addition to the studies reported below, other data on this patient will be presented elsewhere.[5]

J. O. (BIH no. M22290) was a 77 year old man with chronic bronchitis, chronic emphysema and cardiac enlargement. He had had increasing exertional dyspnea and a chronic productive cough for many years. There had been no chest pain. His electrocardiograms, as will be seen below, showed left bundle branch block in addition to changes in the site of impulse formation. On 15 days during an eight-week period the cardiac effects of 62 applications of carotid sinus pressure were observed, 61 on the left and 1 on the right. Numerous long control electrocardiographic observations were made on these and on several other days.

During the following two weeks the patient was hospitalized because of severe respiratory distress and the development of congestive heart failure. He developed a very rapid atrioventricular nodal tachycardia with 2:1 block which did not respond to digitalization and for which quinidine was then administered. As will be described elsewhere,[5] the patient expired shortly after a sudden, quinidine-induced conversion of the tachycardia to a slower supraventricular rhythm. An autopsy revealed coronary artery sclerosis and myocardial fibrosis in addition to evidence of chronic pulmonary disease.

Methods

In each patient a continuous electrocardiogram was recorded on a direct-writing instrument immediately before, during and immediately after the application of manual pressure to either the right or the left carotid sinus. Patients N. S. and J. O. were in a sitting position during each pressure; patient M. S. was semirecumbent. Most of the pressures were of three to five seconds' duration; occasionally the effects of longer pressures (up to 60 seconds) were observed. At least three to four minutes were allowed to elapse between successive pressure tests in any one patient on the same day; this interval has been found to be well beyond the time generally required for the electrocardiographic changes produced by pressure to disappear. Excessive cardiac effects were avoided by watching the electrocardiogram during each pressure. Occasionally, patients N. S. and M. S. noted mild, very transient dizziness in association with carotid sinus pressure. No significant reactions occurred, however, during almost 350 applications of pressure in these three patients.

Electrocardiographic intervals were measured to the nearest 0.01 second. The direct measurement of the time interval between successive beats has been taken to indicate the rate of impulse formation in the various pacemakers. This provides a much more accurate and more sensitive index of change in rate than does the more conventional measurement of the number of beats per minute.

Observations

In each of the three patients it has been possible, repeatedly, with carotid sinus pressure to produce a temporary shift in the control of the heart beat from the dominant site of impulse formation to a lower pacemaker, to identify both pacemakers electrocardiographically, and to measure the two different, practically simultaneous, fundamental rates of impulse formation. No attempt was made to vary the heart rate before pressure. However, spontaneous variations occurred from day to day, and observations were thus made over a fairly wide range of rates. In two of the patients (M. S. and J. O.), the same shift of pacemaker was occasionally observed to occur spontaneously for periods up to a few minutes; the rate of impulse formation in the lower pacemaker after this spontaneous shift could often be compared, within a few minutes, with its rate when the shift was brought about by carotid sinus pressure.

Patient N. S.: Sinoatrial and Slower Atrioventricular Pacemakers

In this patient, the dominant site of impulse formation before carotid sinus pressure, was always in the sinoatrial node: normal P waves followed by supraventricular type QRS complexes (fig. 1, N. S.). Fifteen of the 58 pressures on the right carotid sinus each resulted in a transient shift of the pacemaker to the atrioventricular node: disappearance of the P waves without alteration in the QRS complexes (fig. 1, N. S.). The number of atrioventricular nodal beats observed with any one pressure ranged from two to nine: in only 3 of the 15 pressures were there less than four

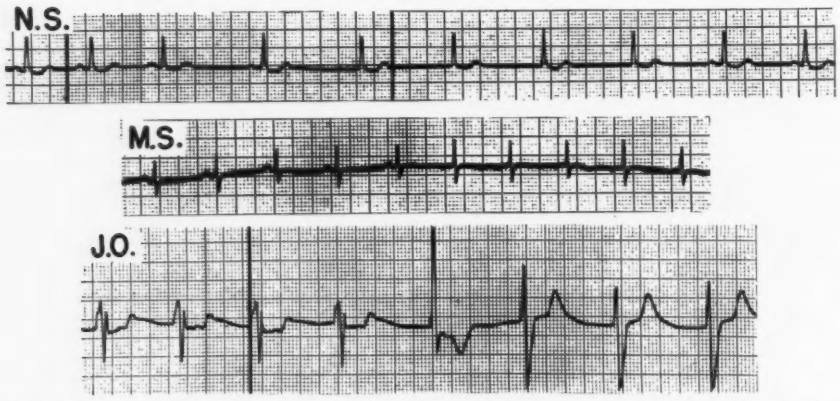

FIG. 1. Changes of pacemaker associated with carotid sinus pressure in each of three patients: patient N. S. (lead II), right carotid sinus pressure was applied between heavy vertical lines; patient M. S. (lead II), 10 seconds after the end of left carotid sinus pressure; patient J. O. (lead V_6), application of left carotid sinus pressure was started at heavy vertical line and was maintained through the period of this tracing. Details of all figures are discussed in the text.

such beats, in 7 of the 15 pressures there were six or more. This effect of reflex vagal stimulation was not observed after left-sided pressure.

Typical cycle length changes of the two pacemakers during carotid sinus pressure are shown in figure 2. In the same figure, for comparison, are shown the changes in sinoatrial cycle length produced by a pressure in which no shift of pacemaker occurred. The shift to the atrioventricular node shown here was preceded, as in every case, by marked prolongation of the sinoatrial cycle length (that is, slowing of rate). The atrioventricular rhythm, once established, persisted after the end of pressure. The first three atrioventricular cycles show the disappearance of the vagal effect on the lower pacemaker, the cycle lengths becoming progressively shorter (that is, the rate increased). During the remainder of the period of atrioventricular rhythm the cycle length leveled off below the sinoatrial control value.

In the upper section of figure 7, the fundamental rates of impulse formation in the sinoatrial and atrioventricular pacemakers are shown for each of the 15 pressures which produced a shift of pacemaker. The average length of the six to eight sinoatrial cycles immediately before a pressure is plotted against the shortest atrioventricular cycle after that pressure. It is

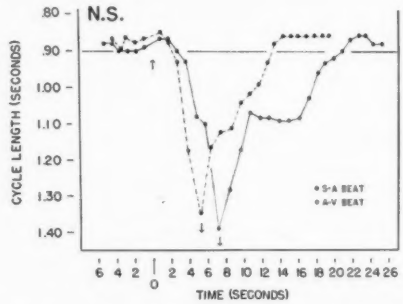

FIG. 2. Changes in cycle length and pacemaker associated with two applications of right carotid sinus pressure in patient N. S. Both pressures were started at ↑ and were stopped at the respective ↓.

apparent that there is a direct relation between these values: as the length of the cycle of impulse formation in the sinoatrial node increases or decreases, there is a corresponding increase or decrease in the cycle of the atrioventricular pacemaker.

Patient M. S.: Sinoatrial and Faster Atrioventricular Pacemakers

The electrocardiographic features of the two pacemakers in this patient are shown in figure 3. The sinoatrial nodal pacemaker has normal P waves and supraventricular type QRS complexes. Sixty-one of the 178 pressures on the left carotid sinus were each followed by a run of beats from a pacemaker high in the

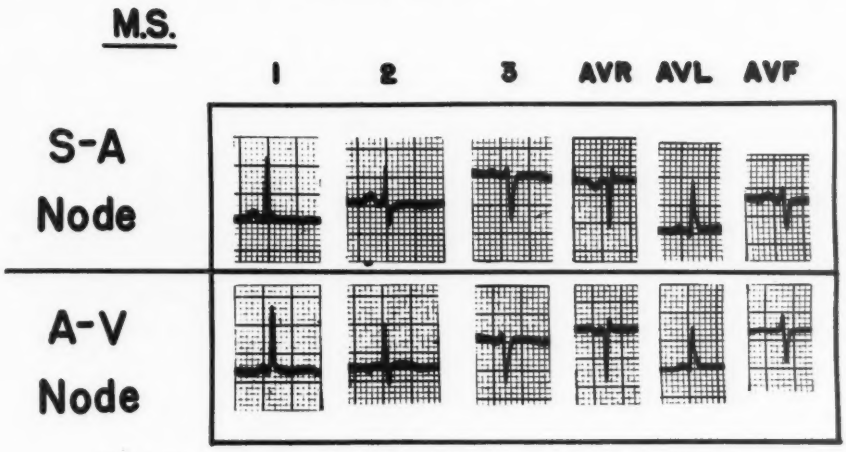

FIG. 3. Electrocardiographic features of two pacemakers in patient M. S.

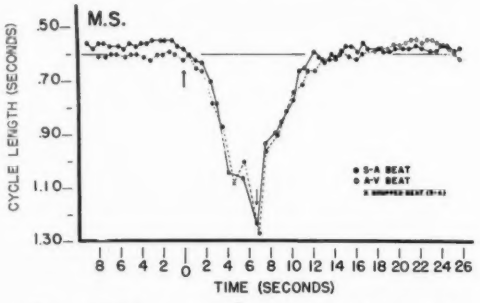

FIG. 4. Changes in cycle length and pacemaker associated with two applications of left carotid sinus pressure in patient M. S. Both pressures were started at ↑ and were stopped at ↓.

atrioventricular node: unchanged QRS complexes with inverted P waves in leads II and III, and upright P wave in lead I. The abrupt shift is shown in figure 1 (M. S.): in consecutive beats the normal upright P wave becomes inverted. Right carotid sinus pressure produced no electrocardiographic changes.

The detailed changes associated with two applications of left carotid sinus pressure, 20 minutes apart on the same day, are shown in figure 4. Both pressures show the same marked prolongation of sinoatrial cycle length (that is, slowing of rate). In one instance the dominant pacemaker, after pressure, remained in the sinoatrial node. In the other instance, however, 11 seconds after the end of pressure, when the sinoatrial cycle length had returned to its control value, there was a sudden shift to the atrioventricular nodal pacemaker at a very slightly faster rate (shorter cycle length). In 61 pressures, the average time from the end of pressure to the transition was 12 seconds (range 6 to 22.5 seconds). In every instance when this shift occurred the sinoatrial rate had returned to its control value and the first atrioventricular nodal cycle was very slightly shorter (that is, faster) than the last sinoatrial cycle. The activity of the atrioventricular pacemaker generally persisted for 5 to 40 seconds. As shown in the run of atrioventricular beats in figure 4, there was sometimes a transient, occasionally more marked, acceleration of rate during atrioventricular control. The cycle length at the end of a run, however, was usually slightly longer than at the beginning (average difference, 0.05 second), and the transition back to sinoatrial control was abrupt.

On many of the days when observations were made, long control electrocardiograms showed repeated spontaneous transitions back and forth between the sinoatrial node and the same atrioventricular nodal pacemaker. The average length of these spontaneous runs of atrioventricular beats varied from day to day; they sometimes lasted for several minutes. They were not preceded by slowing of the sinoatrial rate, nor were they associated with respiration or any apparent possible cause of reflex vagal stimulation, such as swallowing or

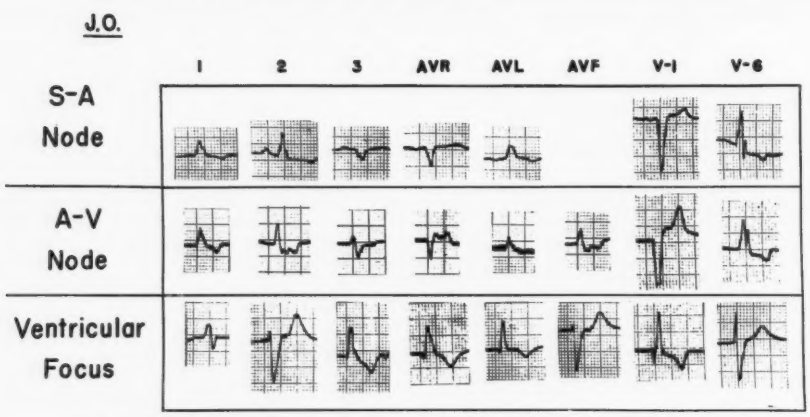

FIG. 5. Electrocardiographic features of three pacemakers in patient J. O.

change of position. In every other respect this spontaneous activity of the atrioventricular pacemaker was identical with its activity following carotid sinus pressure within the same few hours' period: the beginning and the end were abrupt; the first atrioventricular cycle was always shorter (that is, faster) than the last sinoatrial cycle; the last atrioventricular cycle was usually slightly longer (that is, slower) than the first atrioventricular cycle; and the rates of the spontaneous and the pressure-induced atrioventricular activity were the same. Very slight left carotid sinus pressure immediately stopped either spontaneous or pressure-induced activity of the atrioventricular pacemaker and restored sinoatrial nodal control. On those days when the spontaneous runs were long the pressure-induced runs also tended to be long. On days when there was no spontaneous atrioventricular nodal activity, such activity could usually be made to appear after left carotid sinus pressure, and the runs tended to be short.

In the middle section of figure 7 are shown the basic rates of impulse formation in the sinoatrial and the atrioventricular nodes of this patient. For each of the 61 pressure which was followed by a shift of pacemaker, the average length of the six to eight sinoatrial cycles immediately before the pressure is plotted against the cycle length of the first two atrioventricular beats. It is clear that there is a direct relation between the two rates: variations in the cycle of the sinoatrial node are accompanied by corresponding variations in the cycle of the atrioventricular nodal pacemaker.

Patient J. O.: Atrioventricular and Slower Ventricular Pacemakers

The electrocardiographic complexes during sinoatrial control of the heart beat in this patient are shown in figure 5: normal P waves and QRS complexes of left bundle branch block. However, during most of our observations, the dominant pacemaker was in the atrioventricular node (fig. 5): supraventricular type QRS complexes showing left bundle branch block with or without retrograde inverted P waves. Wandering of the pacemaker within the atrioventricular node was indicated by spontaneous changes in the position of the retrograde P waves: sometimes before and sometimes after the QRS complex. Minimal changes in the cycle length (0.03 second) accompanied these shifts, the shorter cycles (that is, faster rates) occurring when the P waves preceded the QRS complexes. Data concerning retrograde conduction and reciprocal beats from the atrioventricular node and from the ventricular focus described below will be presented elsewhere.[5]

Digitoxin was administered in the absence of definite evidence of congestive failure but in an attempt to relieve severe respiratory distress. The patient received 0.6 mg. a day

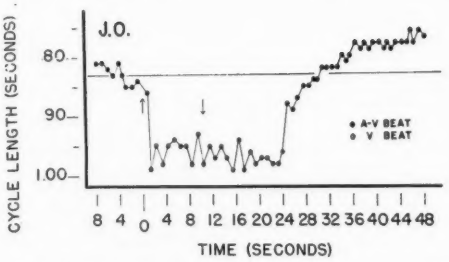

FIG. 6. Changes in cycle length and pacemaker associated with left carotid sinus pressure in patient J. O. Pressure was started at ↑ and was stopped at ↓.

for two days and then 0.2 mg. daily. An electrocardiogram on the day the drug was started showed sinoatrial rhythm; on the fifteenth day of drug therapy atrioventricular nodal control was first observed. Although digitoxin administration was immediately stopped, the activity of the atrioventricular pacemaker continued, and spontaneous sinoatrial control was not observed again until 40 days later. At this time, repeated spontaneous transitions were observed between sinoatrial rhythm and runs of faster atrioventricular nodal activity lasting for 20 to 60 seconds. The differences in rate were very slight, but in every instance the atrioventricular cycle lengths were shorter (that is, faster) than the closely associated sinoatrial cycles. Subsequently, sinoatrial control was observed with no evidence of atrioventricular nodal rhythm. After 17 days, no further digitalis glycoside having been administered, an atrioventricular nodal pacemaker again assumed control of the heart beat, this time at a very rapid rate (around 250 per minute) and with a 2:1 ventricular response.

In 32 of 61 instances, pressure on the left carotid sinus during atrioventricular nodal control produced an immediate shift to an ectopic pacemaker in the left ventricle: QRS complexes markedly different from the supraventricular ones and having the appearance of right bundle branch block (fig. 5). An example of this transition at the start of left carotid sinus pressure is shown in figure 1 (J. O.). The fifth complex, a fusion beat, marks the transition from atrioventricular nodal to ventricular control. Right carotid sinus pressure caused no electrocardiographic changes.

The details of the changes associated with left carotid sinus pressure are shown in figure 6. The shift here from the atrioventricular to the ventricular pacemaker was immediate, with little time for slowing of the atrioventricular rate (that is, prolongation of the cycle). In other instances, definite atrioventricular slowing was observed before the shift occurred. Pressure was continued, on this occasion, for 10 seconds. During the pressure and for 14 seconds after pressure was stopped, the ventricular focus maintained control at a fairly constant rate. There was then an immediate shift back to the atrioventricular pacemaker whose rate progressively rose back to and then above the control level.

On many of the days when observations were made, long control electrocardiograms showed varying degrees of spontaneous activity of the ventricular focus. This ranged from single premature ventricular beats to complete ventricular rhythm such as occurred during carotid sinus pressure. The spontaneous runs of ventricular rhythm sometimes lasted for as long as one minute and were not associated with any apparent extrinsic cause of reflex vagal stimulation. Left carotid sinus pressure had no effect on the rate when applied during the spontaneous runs. On a number of days it was possible to compare the cycle lengths of a pair of spontaneous ventricular beats not separated by an atrioventricular beat, of a spontaneous run of ventricular beats, and of a ventricular run during left carotid sinus pressure: all were the same. The ventricular activity could usually be seen during carotid sinus pressure even on days when it did not appear spontaneously.

The fundamental rates of impulse formation in the atrioventricular node and in the ventricular focus could thus be determined. In the lower part of figure 7, the average of six to eight atrioventricular cycles preceding each of the 32 applications of left carotid sinus pressure is plotted against the average of 6 to 10 ventricular cycles during the respective pressures. There is a direct relation between the

two values: changes in the cycle length of impulse formation in the atrioventricular node are associated with corresponding changes in the cycle of the ectopic ventricular focus.

Discussion

These observations establish a fact of fundamental importance in the normal and pathologic physiology of the cardiac impulse-forming system in man: the physiologic variables which determine the rate of impulse formation in the sinoatrial node also combine to determine the rate of certain active and passive ectopic pacemakers. Several other observers have commented on parallel changes in the rate of the sinoatrial node and of simultaneously active ventricular pacemakers: the idioventricular center in complete heart block[1]; spontaneous ventricular parasystolic foci[2, 3]; and experimental ventricular parasystolic foci.[6] In none of the clinical reports, however, have sufficient data been presented on any one patient to permit a precise comparison of spontaneous changes in the fundamental rates of the two pacemakers.

The fundamental rates of impulse formation of the two pacemakers in each of our three patients could be measured only a few seconds apart. Shifts in control of the heart beat were produced by carotid sinus pressure. The basic rate of the dominant pacemaker could readily be determined before each pressure, and spontaneous variations from day to day provided a fairly wide range of rhythmicity in each case. In order to determine the fundamental rate of impulse formation of the lower pacemaker in each patient, it was essential to distinguish clearly any possible alterations of this rate caused by neurogenic stimuli associated with the carotid sinus pressure.

In patient N. S., reflex vagal stimuli slowed the rate of the sinoatrial node and permitted escape of a slower pacemaker in the atrioventricular node. These stimuli also had a depressing effect on the rate at which the atrioventricular rhythm first appeared. Immediately after the end of pressure, as the vagal effect disappeared, the atrioventricular rate increased, and within a few beats became fairly

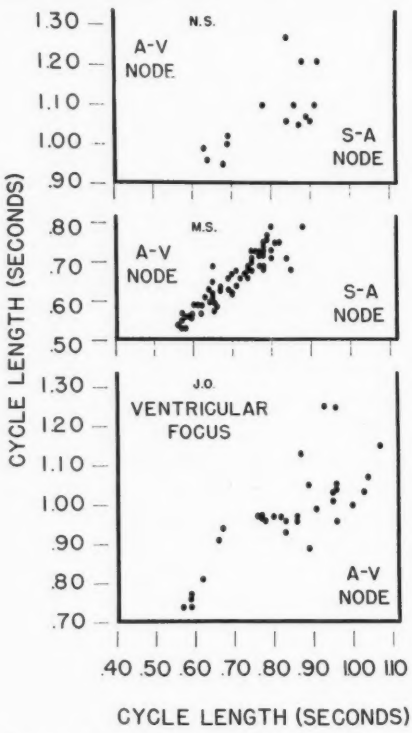

Fig. 7. Relationship between the spontaneously-varying fundamental rates of two practically simultaneous pacemakers in each of three patients.

constant. The occurrence of constant cycle lengths at the end of the majority of the atrioventricular runs suggested that this represented the fundamental rate of the lower pacemaker uninfluenced by vagal or by rebound sympathetic stimulation. In each instance, the shortest (that is, the fastest) atrioventricular nodal cycle was taken as the measure of its basic rate.

In patient M. S., after the end of reflex vagal stimulation there was a shift of the pacemaker from the sinoauricular node to a faster pacemaker high in the atrioventricular node. Several observations indicate that the shift was not a direct effect of vagal stimuli: the change of pacemaker occurred, on the average, 12 seconds after the end of carotid sinus pressure, at a time when the typical vagal slowing of the sinoatrial rate had disappeared; carotid

sinus pressure reapplied during an atrioventricular run always restored sinoatrial control immediately. Such marked lability has been described as a characteristic feature of this type of high atrioventricular nodal rhythm.[7] Experimentally it has been established that reflex vagal stimulation is accompanied by reciprocal sympathetic inhibition[8] and may be followed by rebound of the previously-inhibited sympathetic stimuli.[9] The shift of pacemaker in this patient, like other changes in impulse formation observed after the end of carotid sinus pressure,[10, 11] can be explained by this mechanism. The pressure-induced atrioventricular nodal control clearly represented activation of an already potentially active, faster pacemaker: atrioventricular nodal activity following carotid sinus pressure was identical with the spontaneous atrioventricular nodal activity that often occurred during the same observation period; atrioventricular nodal activity occurred after carotid sinus pressure even on days when it did not occur spontaneously. The first cycle of the pressure-induced activity has been considered to give the best measure of the basic rate of this faster pacemaker. Subsequent, transient acceleration of the atrioventricular rate often occurred, probably as a result of sympathetic stimulation, but by the end of a run the rate was usually slightly below its starting level. It is of interest that the starting rates of pressure-induced and spontaneous runs of atrioventricular nodal activity observed close together on the same day were identical.

In patient J. O., reflex vagal stimulation slowed the rate of the atrioventricular pacemaker and permitted the escape of a slower focus of impulse formation in the left ventricle. The atrioventricular nodal rhythm persisted for 40 days at a normal range of rates and its nature could be determined only toward the end of the period. At this time, before complete sinoatrial control returned, short runs of sinoatrial rhythm interrupted the atrioventricular activity. In these spontaneous transitions, the atrioventricular cycle was always slightly faster than the sinoatrial cycle, indicating an active pacemaker in the atrioventricular node. Although this rhythm developed during digitoxin administration, its persistence for 40 days after the drug was stopped makes it appear unlikely that the disturbance was due to the drug. As further evidence of the spontaneous instability of the impulse-forming system in this patient, it is of interest that, during sinoatrial control following the observations reported here, without further digitalis having been given, an active rhythm again developed in the atrioventricular node, this time at a very rapid rate. The identical features of the spontaneous and pressure-induced ventricular activity indicate that, by depressing the atrioventricular node, the reflex vagal stimulation simply permitted the parasystolic focus to become manifest without the interference of another, faster pacemaker. The fundamental rate of the ventricular focus could readily be determined since it was not affected by the reflex vagal stimuli: during any one pressure the rate of the ventricular focus changed very little; the rate continued unchanged even after the end of a pressure; the transition back to atrioventricular nodal control was always abrupt, and carotid sinus pressure had no effect on the rate when applied during spontaneous ventricular activity.

A comparison of the varying rates of impulse formation in each of the pairs of pacemakers shows similar features in the three individuals. As can be seen in figure 7, the cycle lengths in each instance vary together in a direct and linear fashion. The three lines describing the relationships would have approximately equal slopes of 0.9 to 1.0. This means that, in each case, a given increase or decrease in the cycle length of one pacemaker is accompanied by an approximately equal increase or decrease, respectively, in the cycle length of the other. However, inasmuch as each faster pacemaker has the shorter cycle length, the percentage change in its rate is greater than the corresponding percentage change in the rate of the slower pacemaker (with a longer cycle). In terms of the number of beats per minute, the change is also greater in the faster pacemaker. The difficulty of distinguishing different sites of impulse formation or active and passive

ectopic rhythms, even in the same individual, by the rate alone, is apparent. In each instance, the slowest rate of the faster pacemaker overlaps with the fastest rate of the slower pacemaker. In patient N. S. this overlap is slight, but in patients M. S. and J. O. it includes a rather wide range of rates.

Further observations are necessary to determine whether the same quantitative relationship between the two cycle lengths that was seen in our three patients will pertain to other individuals. It should be noted that once a relationship between the varying rates of two pacemakers in the same individual is established, an excellent opportunity is presented for studying the effects of cardio-active drugs on these pacemakers.

In contrast to these findings, it is known that certain paroxysms of rapid ectopic rhythm may continue for long periods of time at the same rate. They may also recur at varying rates which bear no definite relation to the preceding or succeeding sinoatrial rates. Further observations are necessary to differentiate the ectopic rhythms whose rates are and are not susceptible to change.

Summary

Quantitative observations in three individuals establish the fact that the physiologic variables which determine the rate of impulse formation in the sinoatrial node also determine the rates of certain active and passive ectopic pacemakers.

Sumario Español

En cada uno de tres individuos, la presión al seno carótido produjo un cambio en el pacificador control dominante de las contracciones cardíacas a uno ectópico, mas lento o mas rápido. En cada caso, fué posible medir la frecuencia fundamental de los dos prácticamente simultáneos pacificadores sobre marcadas diferencias en frecuencia: se encontró, una relación directa y linear.

REFERENCES

[1] Gilchrist, A. R.: The effects of bodily rest, muscular activity, and induced pyrexia on the ventricular rate in complete heart-block. Quart. J. Med. **3:** 381, 1934.

[2] Kaufmann, R., and Rothberger, C. J.: Beitrage zur Entstehungsweise extrasystolischer allorhythmien. Ztschr. ges. exper. Med. **7:** 199, 1919.

[3] Scherf, D., and Boyd, L. J.: Three unusual cases of parasystole. Am. Heart J. **39:** 650, 1950.

[4] Linenthal, A. J.: Quantitative studies in man of the cardiovascular effects of reflex vagal stimulation produced by carotid sinus pressure. I. Localization of an increased effect in a patient with angina pectoris. Circulation **5:** 81, 1952.

[5] —: In preparation.

[6] Scherf, D., and Chick, F. B.: Experimental parasystole. Am. Heart J. **42:** 212, 1951.

[7] —, and Harris, R.: Coronary sinus rhythm. Am. Heart J. **32:** 443, 1946.

[8] Bronk, D. W., Ferguson, L. K., and Solandt, D. Y.: Inhibition of cardiac accelerator impulses by the carotid sinus. Proc. Soc. Exper. Biol. & Med. **31:** 579, 1934.

[9] Sherrington, C. S.: The integrative action of the nervous system. New York, Scribners, 1906.

[10] Weiland, W.: Experimentelle untersuchung an saugetheirherzen uber den fordernden einfluss der vaguserregung auf das suftreten von extrasystolen. Ztschr. exper. Path. u. Therap. **9:** 486, 1911.

[11] Linenthal, A. J.: Unpublished observations.

The Spatial QRS and T Vector in 178 Normal Middle-Aged Men

Body Weight, Height, Relationship of QRS and T and Preliminary Standards

By Ernst Simonson, M.D., and Ancel Keys, Ph.D.

From the means and standard deviations of the coordinates of the spatial QRS and T vectors in 178 normal middle-aged men, preliminary normal range limits were calculated for the total group, three positional subgroups, and three relative body weight groups. The superiority of spatial vector analysis over analysis of the scalar electrocardiogram made it possible for the first time to investigate meaningful correlations between electrocardiographic variables, such as the relationship between the magnitude of QRS and T vectors. The relationship between fundamental constitutional variables and spatial vectors was also investigated as background necessary for the diagnostic use of spatial vectors.

ALTHOUGH the interest in the spatial vectorcardiogram is increasing, no adequate normal standards are yet available. One reason for this is the descriptive nature of presentation of the normal data[1] which is not suitable for quantitative evaluation. While in photographic records from oscilloscopes the projection in different planes can be measured,[2, 3] these values do not give the spatial vector, although it can be visualized or calculated.

A simple method has been recently described[4] which allows construction of the spatial QRS and T vector from the conventional electrocardiogram. The spatial vectors are expressed in terms of a horizontal angle (H°, azimuth), vertical angle (V°, elevation), and magnitude (Mag). The angle (dA°) between the spatial mean QRS and T vectors also is measured. Thus, a total of seven items replaces about 40 electrocardiographic items in the quantitative analysis of a nine lead electrocardiogram,[5] and, at the same time, correction is made for a major source of error in the analysis of the scalar electrocardiogram: the varying and unknown projection angle of spatial vectors on any given lead. Using this method, the means, standard deviations, and expected normal limits of a fairly large sample of middle-aged men were calculated, and an investigation was made on the effect of some important constitutional variables and correlations between the items of vector analysis.

Method

The analysis of the spatial QRS and T vectors is based on the determination of their direction and magnitude in the frontal plane from the peak deflections of the R wave, S wave, and T wave in leads I and III (using the principle of Einthoven's method for measurement of axes and manifest potentials), and on the determination of the direction of the vectors in the horizontal plane from their null points in the precordial leads. This vector corresponds to the "mean spatial vector" in some other recent studies.[3a, b]

All leads are taken at the fifth intercostal level, but in the same vertical positions as the conventional precordial leads. Additional leads to the right of $V_{1(5)}$ or to the left of V_6 are taken, when necessary, to include the transitional zones (null points) of the QRS complex and the T wave. Further details of the method are described in the original communication.[4]

The 0 to 180 degree reference line for the angle H° in the horizontal plane is a transverse line, parallel to lead I, passing through a hypothetic center of the heart from left (0 degrees) to right (± 180 degrees), with the positive hemisphere in front and the negative hemisphere in the back. The vertical angle, V°,

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TABLE 1.—*Spatial QRS and T vectors, Means (M.) and Standard Deviations (S.D.), in Five Relative Body Weight Groups (A = Marked Underweight, B = Moderate Underweight, C = Normal Weight, D = Moderate Overweight, E = Marked Overweight)*

Group	N	QRS Vector						T Vector						dA°	
		H°		V°		Mag		H°		V°		Mag			
		M.	S.D.	M.	S.D.	M.	S.D.	M.	S.D.	M.	S.D.	M.	S.D.	M.	S. D.
A	25	−30.4	23.96	52.0	32.35	9.1	3.79	39.5	15.25	45.0	17.24	3.0	1.09	52.8	24.7
B	37	−24.1	14.32	39.8	19.19	10.1	3.69	46.2	15.69	49.1	15.76	3.6	1.09	45.7	17.8
C	54	−21.3	20.64	55.4	24.68	10.6	2.87	39.8	12.75	67.9	18.02	3.5	1.24	56.4	22.1
D	39	−23.4	20.24	61.3	23.37	9.5	3.21	47.5	14.77	70.4	13.56	3.2	1.22	64.9	21.3
E	23	−10.5	27.20	66.4	24.38	9.8	2.79	44.0	16.44	72.4	15.71	3.3	1.35	52.7	20.7
Total.....	178	−22.2	21.35	54.2	26.02	9.9	3.26	42.3	14.84	61.9	19.34	3.4	1.20	55.0	22.0

H° = horizontal angle, V° = vertical angle, Mag = magnitude, dA° = spatial angle between QRS and T vector.

is the angle between the vector and a vertical projection through the hypothetic center of the heart onto the horizontal plane. The "elevation" in analytic geometry is 90–V°. The reason for the definition of V° is simplicity of measurement and avoidance of negative values for V°. The angle between spatial vectors (dA°) is positive when the rotation from the first to the second vector, in their sequence in the cycle, is in clockwise direction as viewed from above.

The subjects were 178 middle-aged men, with a mean age of 53.23 years ± 2.88. They were carefully screened as to absence of any objective or subjective signs of disease from detailed clinical and laboratory examination on the day of the electrocardiographic study. This group has been annually examined for four consecutive years, so that, compared with other "normal" groups, the subjects were defined as to state of health with more than ordinary precision. The total group was subdivided into five weight groups (A, < 85 per cent standard weight, mean 79.54 ± 4.18; B, from 86 to 95 per cent standard weight, mean 91.03 ± 2.45; C, from 96 to 105 per cent standard weight, mean 100.55 ± 2.56; D, from 106 to 115 per cent standard weight, mean 109.33 ± 2.55; E, > 115 per cent standard weight, mean 122.00 ± 6.65). The mean relative body weight of the total groups was 100.32 per cent, with a standard deviation of ±13.06. The standard weight is estimated from height and age using the standards of the medicoactuarial Mortality Investigations.[6]

The group was also divided into three subgroups according to the electrical heart position: group I, QRS axis in the frontal plane with angle α less than 20 degrees; group II, α between 20 and 60 degrees; group III, α above 60 degrees. Group I corresponds approximately to horizontal plus semihorizontal, group II to intermediate, and group III to vertical plus semivertical heart position as determined from unipolar limb leads. Since the relative body weight is related to the QRS axis,[7] the relative body weight differs in the positional groups (group I: mean 105.18 ± 12.36; group II: 100.66 ± 12.91; group III: 94.72 ± 12.2). The subdivision into weight and positional groups is, therefore, not independent, and the positional trends may be considered in part, but not entirely, as concealed weight trends and vice versa.

RESULTS

1. *Relative Body Weight.* Table 1 shows the means (M.) and standard deviations (S.D.) of the QRS and T vectors in the five weight groups A to E and in the total group. The increase of QRS–V° and T–V° with increasing relative body weight agrees with the shift to the left of the QRS and T axis in the frontal plane found in an earlier investigation.[7] The left axis shift is, of course, the projection of the change of V° on the frontal plane, and, for this reason, V° is the fundamental variable. There is also a definite shift of QRS–H° and some shift of T–H° and dA° in clockwise rotation, as viewed from above, with increasing relative body weight. On the other hand, there is no effect of relative body weight on QRS–Mag. The changes of the R wave with body weight found in the analysis of scalar electrocardiograms in various leads,[7] therefore, are due to a change of the direction of the QRS vector and not to a change of its magnitude.

For statistical evaluation of the effect of relative body weight on the spatial mean QRS and T vectors, the weight groups A + B were compared with the weight groups D + E (table 2). The numbers of subjects in these

TABLE 2.—*Means (M.) and Standard Deviations (S.D.) of Spatial Angles of the QRS and T Vector in 62 Underweight (A + B) and 62 Overweight (D + E) Middle-Aged Normal Men, the Mean Difference (M.D.) between These Groups and Their Statistical Significance, as Indicated by the t Value and the Level of Expectancy, p*

Group	QRS-Vector				T-Vector				dA°	
	H°		V°		H°		V°			
	M.	S.D.	M.	S.D.	M.	S.D.	M.	S.D.	M.	S.D.
A + B	−26.66	13.88	44.70	25.80	40.52	15.41	47.42	16.36	48.55	21.00
D + E	−18.63	23.70	63.15	23.68	46.16	15.37	71.16	14.30	60.39	21.78
M.D.	8.03		18.45		5.64		23.74		11.84	
t	2.30		4.15		2.04		8.60		3.08	
p	0.02		0.001		0.05		0.001		0.01	

combined weight groups were identical. The mean differences of all spatial angles between the underweight (A + B) and overweight (D + E) groups were statistically significant, though at different levels of expectancy. Of particular interest is the high level of statistical significance for the difference in dA°, since this cannot be due to a positional effect.

The magnitude of the T vector showed a maximum for group B, with a statistically significant difference ($p = 0.05$) from group A ($t = 2.0$), but not from group E. The significant changes of the direction of spatial QRS and T vectors found in this series substantiate and amplify the earlier results of the effect of body weight on the scalar electrocardiogram.[7]

In the total group, as well as in all weight groups except B, the standard deviations of H° and V° are larger for the QRS vector than for the T vector, which is somewhat surprising, since in experimental and many abnormal situations the T wave is much more easily and more frequently changed than the QRS complex. This means that a high intraindividual variability does not necessarily imply a high interindividual variability. It is of interest that in the material of Burch and co-workers,[3] also, the scatter of the projections of the maximum T vector in the horizontal and sagittal plane is less than that of the maximum QRS vector, although these authors do not comment on this point.

However, the variability of all spatial angles is quite large, in confirmation of the rather wide range limits in the frontal (Einthoven) plane[8] and in the horizontal plane (precordial leads[9]). On the other hand, the variability of QRS– and T–Mag is relatively small, which will permit a more precise differentiation between normal and abnormal voltage than has been possible with the scalar electrocardiogram.

2. *Height and Chest Circumference.* Since the relative body weight, expressed as a percentage of standard weight, is an indirect index for the height-weight ratio, or the weight per centimeter of height, circumference as well as height are included in this formulation. In order to investigate whether height and circumference are important variables independent of the relative body weight, the 21 shortest and tallest subjects, and 19 subjects with smallest and largest chest circumference were compared (table 3). It would have been advantageous to select for this comparison the subjects of one relative body weight group, but the number of subjects in any of the weight groups was too small for this purpose.

The mean relative weights of the 21 shortest and 21 tallest men differed only by 5.5 per cent, and this difference was not statistically significant. We compare, therefore, essentially men of normal standard weight, since the means were not significantly different from 100 per cent. The height had no effect on the direction of vectors, but the magnitude of both the QRS and T vector was definitely greater in the smaller men (23.6 per cent for the QRS vector and 11.4 per cent for the T vector). The difference was statistically significant (for QRS–Mag, $p < 0.05$; for T–Mag, $p < 0.01$, as calculated by means of the t test). The

TABLE 3.—*Effect of Height and Chest Circumference on the Spatial QRS and T Vector*

Group, N		Height cm.	Rel. St. W. %	QRS-Vector			T-Vector			dA°
				H°	V°	Mag	H°	V°	Mag	
Height										
21 shortest	M.	166.6	103.3	−18.8	57.3	*10.8*	41.0	68.7	*3.35*	55.0
	S.D.	2.66	11.38	21.96	26.31	2.59	12.58	18.17	1.24	16.48
21 tallest	M.	186.7	97.8	−26.2	53.6	*8.2*	43.6	57.3	*2.97*	58.4
	S.D.	3.19	14.28	17.72	27.16	3.27	17.47	20.99	1.39	23.21
		Circum. cm.								
Chest										
19 smallest	M.	86.5	81.8	−25.8	46.3	9.8	41.9	48.8	*3.3*	50.72
	S.D.	1.89	6.63	22.29	30.59	3.79	15.81	16.77	0.97	19.28
18 largest	M.	110.6	120.9	−10.6	70.5	9.1	45.4	78.2	*2.5*	52.3
	S.D.	2.18	9.62	29.30	19.96	2.86	15.94	16.22	0.85	22.88

greater amplitude in shorter men could be explained by a higher ratio of heart volume/chest volume in shorter men. While this hypothesis is conjectural at the present time, we are inclined to believe that the effect of height is due to extracardiac rather than to cardiac variables.

It was not possible to separate the chest circumference from relative body weight. There was a statistically highly significant difference between the relative body weight of the subjects with the smallest and largest chest circumference, which was nearly as great as a comparison of the most overweight and most underweight individuals would have been. Consequently, the difference of QRS–H°, QRS–V°, T–H°, and T–V° are similar to the differences between weight groups A and E in table 1. There is, however, a slightly greater amplitude of QRS–Mag and, even more so, of T–Mag in the individuals with smaller chest circumference. The difference of QRS–Mag did not reach the level of statistical significance, but that of T–Mag was significant at the 0.01 level. The direction of changes is the same as that between the smallest and tallest men, and may also be due to a higher ratio of heart volume/chest volume in the men with smaller chest circumference.

3. *Electrical Heart Position.* It seemed to be of interest to investigate the effect of the conventionally defined electrical heart position on the mean spatial vectors (table 4). Subdivision into three positional groups (I: horizontal, semihorizontal; II: intermediate; III: vertical, semivertical) shows, as expected, a highly significant decrease of QRS–V° and T–V° in the above order. Since the QRS axis in the frontal plane was used for the subdivision of positional groups, the difference of QRS–V° between groups I and III is greater than that of T–V°, but both were statistically highly significant ($p = 0.001$). The marked reduction of the variability (S.D.) of QRS–V° in any positional group, compared with that of the total group or the five weight groups (table 1) was expected. Surprisingly enough, there was only a slight reduction of the S.D. for T–V°.

Electrical position in the frontal plane had no effect on QRS–H°, T–H° or QRS–Mag, but there was a consistent ($p = 0.05$) increase of T–Mag from horizontal to vertical position. The increase of dA° from vertical to horizontal position was statistically highly significant ($p = 0.001$), even more so than the difference of dA° between the underweight and overweight groups (table 2).

The standard deviation of QRS–H°, QRS–V° and dA° was smallest in group III. The difference of the standard deviations between group I and III was highly significant ($p < 0.01$) for all three angles, as calculated by means of the F test, and this was true also for the difference of the standard deviation of QRS–V° between groups II and III. The smaller variability of the direction of the mean spatial

TABLE 4.—*Spatial QRS and T Vectors of 178 Normal Middle-Aged Men, Subdivided in Three Positional Groups (I: Vertical and Semivertical, 48; II: Intermediate, 84; III: Semihorizontal and Horizontal, 46); Means (M.), Standard Deviations, (S.D.)*

Group	QRS Vector						T Vector						dA°	
	H°		V°		Mag		H°		V°		Mag			
	M.	S.D.	M.	S.D.	M.	S. D.	M.	S.D.	M.	S.D.	M.	S.D.	M.	S. D.
I	−22.6	23.19	85.0	14.94	10.0	3.52	42.3	14.13	78.5	14.93	3.17	1.09	68.4	24.47
II	−19.8	22.48	53.8	13.97	9.5	3.02	41.7	13.81	60.2	16.80	3.35	1.26	53.0	20.14
III	−26.3	16.46	23.5	6.96	10.7	3.35	43.3	17.44	47.7	14.58	3.64	1.19	44.9	15.57

QRS vector in vertical hearts is of importance for normal standards. It is probable that abnormal variations can be recognized more easily or earlier in vertical hearts.

4. *Physiologic Correlates.* In spite of the approximate nature of this method of spatial vector analysis, it approaches the actual situation more closely than conventional analysis of scalar electrocardiograms. This and the drastic reduction of electrocardiographic items makes it possible for the first time, to attempt a meaningful statistical evaluation of correlations between electrocardiographic variables.

The first question to be examined was that of the relationship between the elevation and azimuth angles (V° versus H°). It was interesting that in neither QRS nor T was there any correlation at all between V° and H°; apparently the factors responsible for V° and H° are largely independent in both of the major deflections.

The angle (dA°) between the spatial QRS and T vectors is of particular interest because it increases in ventricular ischemia. It was found that there is no correlation between dA° and either QRS–H° or T–H°, but when the analysis was made with the vertical angle (V°) the result was highly significant. The coefficient of correlation between QRS–V° and dA° was $r = 0.412$ ($t = 6.00$), while that between T–V° and dA° was $r = 0.440$ ($t = 6.5$). This agrees with the statistically highly significant difference of dA° between the extreme positional groups I (mean QRS–V° = 85 degrees) and III (mean QRS–V° = 23.5 degrees) indicated in table 4. QRS–V° and T–V°, like dA°, cannot be indexes of position alone but must reflect some electrophysiologic property.

Analysis of the correlation between QRS–Mag and T–Mag has some importance because of the bearing on one of the oldest and most controversial topics in electrocardiography: the relationship between the QRS complex and the T wave. Katz's excellent review[10] of this problem lists about 500 references as early as 1928, and since then the question has been given greater emphasis by the concept of the ventricular gradient.

Figures 1*A*, *B* and *C* show on logarithmic paper the scatter diagrams of QRS–Mag versus T–Mag in three groups of subjects segregated according to the angle (dA°) between the vectors. In the men with dA° smaller than 45 degrees and in those with dA° between 45 degrees and 65 degrees there were highly significant correlations of $r = 0.35$ ($t = 2.84$, $p = 0.01$) and $r = 0.51$ ($t = 4.5$, $p < 0.001$), respectively. In contrast, in the men with a large angle between the vectors (dA° > 65°), there was no statistically significant correlation ($r = 0.18$).

5. *Normal Standards.* The expected high and low normal limits were calculated from the means and standard deviations for 95 per cent of the normal population for the three weight groups A + B, C, D + E (table 2), the three positional groups I, II, and III (table 4), and the total group. Any value exceeding these limits is probably abnormal. More liberal or more conservative normal range limits can easily be calculated from tables 2 and 4.

The normal limits for QRS–Mag and T–Mag were calculated from the total group, since the

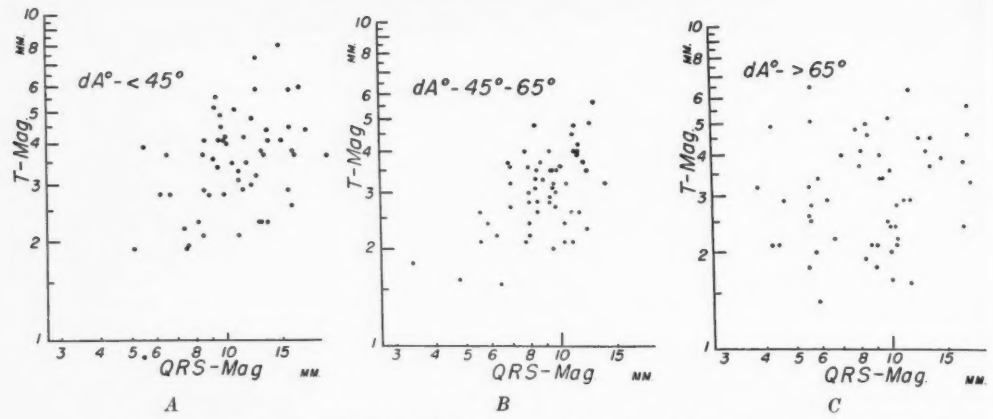

FIG. 1. Scatter diagram of QRS-Mag (abscissa) versus T-Mag (ordinate) in men (*A*) with dA° < 45 degrees, (*B*) with dA from 45 to 65 degrees, and (*C*) with dA° < 65 degrees. Presence of correlation in *A* and *B*, absence in *C*.

relative body weight or electrical heart position did not affect QRS–Mag, and the differences in T–Mag, although statistically significant, were too small to be considered for the normal range limits. Table 5 shows the normal range limits for QRS–Mag and T–Mag.

The range limits for the directions of the QRS and T vector and dA° were calculated for the three weight groups and positional groups (table 6).

The values with comparatively narrow range limits are underlined; it will be advantageous to use them as reference for those particular subgroups. For T–H°, the limits for all six groups are quite similar.

Minor discrepancies of the range limits between the various subgroups of table 6 and the total group (not included in table 6) are due to the fact that each group represents a differently defined sample of the population. The total group is not truly representative for any general population, since the proportion of underweight and overweight people is greater in our sample. For this reason, the limits for the subgroups in table 6 are probably preferable to those calculated for the whole group. However, the subgroups were too small to analyze possible skewness of distribution. Calculation of normal range limits from the standard deviation is based on the assumption of symmetric Gaussian distribution. The limits as presented in tables 5 and 6, therefore, have a preliminary character. While the total group was large enough for analysis of skewness, such analysis was not believed to be useful in view of the greater proportion of underweight and overweight people compared with general population. Since the relative body weight is one of the important variables for the spatial QRS and T vectors, a possible skewness in our sample could not be applied to general population.

It is of interest to compare the range limits for the QRS axis and T axis in the frontal plane with the range limits of QRS–V° and T–V°. Such a comparison was made for weight group C. Since projection of a spatial angle in any plane will foreshorten the angle, it is important that the 98 per cent range limits of the QRS axis for weight group C, taken from an earlier study,[8] are larger (136.6 degrees) than those of QRS–V° (116 degrees), while the range limits of the T axis and T–V° were practically identical (86.4 degrees versus 84.8 degrees).

The range limits of regional distribution of the RST pattern at the level of the fifth intercostal space in three positional groups, as shown in figure 1 of an earlier series,[9] compare very well with the range limits of QRS–H°. In other words, the range limits for the spatial QRS and T vectors are not larger than would be expected from the analysis of scalar electrocardiograms. In view of this situation it is important that the range limits of the angle

TABLE 5.—*High (H) and Low (L) Limits of QRS–Mag and T–Mag; for 95 per cent of Normal Population, Calculated from Total Group in Terms of Standardized mm. Deflection (1 mm. = 0.1 mv.)*

Item	H	L
QRS–Mag	16.4	3.4
T–Mag	5.8	1.0

TABLE 6.—*High (H) and Low (L) Limits of Spatial Angles of the QRS and T Vectors, for 95 per cent of Normal Population, Calculated from Three Relative Body Weights and Three Positional Groups. Values with Comparatively Narrow Range Limits Are Italicized*

Groups	QRS-H°		QRS-V°		T-H°		T-V°		dA°	
Body Weight	H	L	H	L	H	L	H	L	H	L
A + B	*+10*	*−54*	96	0	71	10	80	15	*+91*	+7
C	*+20*	*−63*	105	4	65	14	104	32	+101	+12
D + E	*+29*	*−66*	110	16	77	15	100	43	*+110*	*+23*
Pos.										
I (H + SH)	+24	−69	*115*	*55*	71	14	*108*	*49*	+117	+20
II (I)	+25	−65	*82*	*26*	69	14	*94*	*26*	*+93*	*+13*
III (V + SV)	+7	*−59*	*37*	*10*	72	15	77	*19*	*+76*	*+14*

dA° between the spatial QRS and T vectors are fairly wide. Previous literature[11] limited to the projection of that angle on the frontal plane gave the impression of a relatively small angle. We mentioned already, that the projection of a spatial angle on the frontal plane will always show foreshortening. Limitation to the frontal plane, therefore, might lead to a false diagnosis of ventricular ischemia. It should be noted, however, that the sign of dA° is positive in all groups. Reversal of the sign of dA° appears to be an important diagnostic criterion in some pathologic conditions, for instance, in right ventricular preponderance.

COMMENT

While the normal range limits, as presented in tables 5 and 6, are preliminary and should be corrected when larger material will be available, they are useful at the present time because no other normal standards for spatial vectors have yet been published. Although our group is too small for definitive normal standards, it is believed to be large enough to be fairly representative. In other words, we do not expect very radical changes when additional material, drawn from the same type of population (white, middle-aged, "white-collar" workers) will be available. The standards definitely do not apply to younger age groups.* Differences from other population groups, different in race, climate, diet, occupation, and other factors, are possible, and further studies in this respect are contemplated. For the time being, however, it is suggested that the normal standards as given in tables 5 and 6 for the middle-aged male population of the United States be used.

The statistically highly significant difference of dA° between overweight (mean dA° = 60.39 degrees) and underweight (mean dA° = 48.55 degrees) persons (table 2) is interesting. It is known that ventricular ischemia tends to increase dA°. In a previous study[7] it was found that increasing relative body weight produces electrocardiographic trends in the direction of relative left ventricular preponderance in middle-aged subjects. Since the relative body weight affected the electrocardiogram in a younger age group to a far lesser extent, it was concluded that the electrocardiographic weight trends in middle-aged people could not be due to positional effects alone. The difference of dA° between overweight and underweight persons strengthens this conclusion, since dA° should not change when the position alone is changed. This has been demonstrated in model experiments by Boden.[12]

Relative obesity, therefore, increases dA° independent of positional changes, and this effect is in the direction of relative left ven-

* It would have been of interest to compare with our group the maximum QRS and T vectors in Burch and co-workers'[3] younger age group of 71 male and 4 female medical students. The maximum vector, as measured as projection on the sagittal and horizontal plane from oscillographic records, is not identical with the vector as defined in this study, but the difference is probably not large. However, it was not possible to construct the individual vectors from the scatter diagrams of their projections in two planes, and, also, no standard deviations were given. Moreover, the scatter in their figure 4 is smaller than in larger groups of young men.[7] This means probably that their group was preselected and not sufficiently representative for normal standards. Actually, no such claim was made.

tricular ischemia. The question arises whether a larger dA° might not represent, in fact, a slight degree of ischemia. Although this is, at the present time, purely hypothetic, it might be compatible with the higher incidence of degenerative heart disease in obese subjects. If this possibility is admitted, the question arises whether the standards for overweight subjects, as presented in tables 2 and 6, are *desirable* values. This problem is important, but no definite answer can be given at the present time.

From a theoretic point of view, we consider the demonstration of a correlation between the mean QRS and T vectors, dependent on the spatial angle dA° between these vectors, to be the most interesting finding. It shows the superiority of spatial vector analysis over conventional electrocardiographic analysis. By means of separation into groups according to the dA° it was possible to obtain a highly significant correlation. In the analysis of scalar electrocardiograms, the error of projection of spatial vectors on any given lead, and the inaccessibility of dA°, has obscured the relationship between QRS complex and T wave. By means of spatial vector analysis, therefore, it was possible to decide a controversial issue in the electrocardiographic literature on a fairly safe basis.

The correlation was statistically significant for groups with dA° $<$ 65 degrees, but the correlation coefficient is too low to predict T–Mag from the QRS–Mag or vice versa with any reliability for a given individual. The dependence of the correlation on dA° suggests that dA° itself is an important variable not only for the direction, but also the magnitude of the mean spatial QRS and T vectors. A high dA° ($>$ 65 degrees), even within physiologic limits, is of importance since it tends to abolish the physiologic correlations between QRS and T. It will be recalled that a high dA° is more common in overweight than in underweight persons.

The present investigation is concerned with amplitudes and not with areas, but the absence of a correlation between QRS and T at high dA° has some bearing on the validity of the ventricular gradient concept, as will be shown in another communication.[13]

The validity of this and other methods of spatial vector analysis depends on the validity of Einthoven's dipole concept. Recent investigations[14–16] have revealed that in normal as well as in the majority of abnormal electrocardiograms the dipole theory is in conformity with all findings in the great majority of cases.

In an approximate method like this a certain sacrifice of accuracy in favor of simplicity is unavoidable. One of the limitations of this method, discussed in the original communication,[4] is the lack of precision in the definition of amplitudes due to phase differences in various leads. Therefore, it would be difficult to obtain the same amplitudes from oscilloscopic loop records. However, in normal electrocardiograms and in many abnormal electrocardiograms the phase differences are not large (depending on the contour of the loop), so that the amplitudes as defined by this method will be quite close to the spatial instantaneous maximum amplitudes which could be obtained from oscilloscopic loop records in the frontal and horizontal plane. For their construction this method of vector analysis could be conveniently used with only slight modifications. It should be noted, however, that such analysis of the instantaneous maximum vectors has not yet been made; in the available literature on oscilloscopically recorded loops only photographs of the loops, usually in three planes, were presented.

Summary

1. The spatial QRS and T vectors of 178 normal middle-aged men were measured by means of a newly developed method and were expressed in terms of a horizontal angle (H°, azimuth), vertical angle (V°, elevation), magnitude (Mag), and the angle (dA°) between the spatial QRS and T vectors.

2. The vertical angle V° both of the spatial QRS and T vector increases significantly with the relative body weight, and there is also a shift of QRS–H°, and T–H° in clockwise rotation as viewed from above.

3. The increase of dA° with relative body

veight cannot be explained by positional hanges.

4. There is no relationship between relative ody weight and QRS–Mag or T–Mag, but oth vectors are significantly larger in the horter than in the taller subjects.

5. Electrical position in the frontal plane as no effect on QRS–H°, T–H°, or QRS–Mag, ut there is a consistent increase of T–Mag and highly significant decrease of dA° from horizontal to vertical position.

6. The interindividual variability of QRS–H°, QRS–V°, and dA° is smallest in the group with vertical and semivertical hearts.

7. Contrary to expectation, the interindividual variability of H° and V° is larger for the QRS vector than for the T vector.

8. Preliminary upper and lower normal limits for the spatial QRS and T vectors, calculated from the standard deviation for 95 per cent of the normal population of which these men are samples, are presented for different weight and positional groups.

9. There is no interindividual correlation between QRS–V° and QRS–H°, between T–V° and T–H°, between QRS–H° or T–H° and dA°, but there is a highly significant correlation between QRS–V° and dA°, and between T–V° and dA°.

10. There is a highly significant correlation between QRS–Mag and T–Mag for individuals with dA° < 65 degrees, but the correlation is absent for larger dA°.

11. The significance of the results for theoretic and clinical electrocardiography is discussed.

Sumario Español

De los promedios y las desviaciones standard de los coordenados de los espaciales QRS los vectores T en 178 hombres de edad adura, límites preliminares de los valores ormales para el grupo total fueron calculados, es subgrupos posicionales, y tres grupos de eso relativo del cuerpo. La superioridad del nálisis espacial de vectores sobre el análisis el electrocardiograma numérico ha hecho osible por primera vez la investigación de orrelaciones significativas entre variantes lectrocardiográficas, como la relacción entre la magnitud de los vectores QRS y T. La relacción entre las variantes constitucionales fundamentales y los vectores espaciales fué también investigada como una base necesaria para el uso diagnóstico de los vectores espaciales.

REFERENCES

[1] Scherlis, L., Lasser, R. P., and Grishman, A.: Spatial vectorcardiography: VI. The normal vectorcardiogram. Am. Heart J. **41:** 494, 1951.

[2] Conway, J. P., Cronvich, J. A., and Burch, G. E.: Observations on the spatial vectorcardiogram in man. Am. Heart J. **38:** 537, 1949.

[3] Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Studies of the spatial vectorcardiogram in normal man. Circulation **7:** 558, 1953.

[3a] Grant, R. P.: The relationship of unipolar chest leads to the electrical field of the heart. Circulation **1:** 878, 1950.

[3b] —: Spatial vector electrocardiography. A method for calculating the spatial electrical vectors of the heart from conventional leads. Circulation **2:** 676, 1950.

[4] Simonson, E.: A spatial vector analyzer for the conventional electrocardiogram. Circulation **7:** 403, 1953.

[5] —, Brozek, J., and Keys, A.: Variability of the electrocardiogram in normal young men. Am. Heart J. **38:** 407, 1949.

[6] Association of Life Insurance Medical Directors and Actuarial Society of America (1912). Medico-actuarial mortality investigation. New York, Vol. 1.

[7] Simonson, E., and Keys, A.: The effect of age and body weight on the electrocardiogram of healthy men. Circulation **6:** 749, 1952.

[8] Simonson, E.: Criteria of normality in clinical electrocardiography. Bull. Univ. Minnesota Hosp. **23:** 371, 1952.

[9] —: The distribution of cardiac potentials around the chest in one hundred and three normal men. Circulation **6:** 201, 1952.

[10] Katz, L. N.: Significance of T wave in electrogram and electrocardiogram. Physiol. Rev. **8:** 447, 1928.

[11] Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography. Philadelphia, Blakiston, 1951. P. 149.

[12] Boden, E.: Elektrokardiographie für die ärztliche Praxis. Darmstadt, Steinkopff, 1952. P. 287.

[13] Simonson, E., Schmitt, O. H., Dahl, J., and Fry, D.: The theoretical and experimental bases of the frontal plane ventricular gradient and its spatial counterpart. Am. Heart J. (In press.)

[14] Schmitt, O. H., Levine, R. B., and Simonson, E.: Electrocardiographic mirror pattern studies.

I. Experimental validity tests of the dipole hypothesis and of the central terminal theory. Am. Heart J. **45:** 416, 1953.

[15] LEVINE, R. B., SCHMITT, O. H., AND SIMONSON, E.: Electrocardiographic mirror pattern studies. II. The statistical and individual validity of the heart dipole concept as applied in electrocardiographic analysis. Am. Heart J. **45:** 500, 1953.

[16] SIMONSON, E., SCHMITT, O. H., LEVINE, R. B., AND DAHL, J.: Electrocardiographic mirror pattern studies. III. Mirror pattern cancellation in normal and abnormal subjects. Am. Heart J. **45:** 655, 1953.

CLINICAL CONFERENCES

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Digitalis Intoxication

Arranged by ARTHUR C. DEGRAFF, M.D.

Since 1946, when the Veterans Administration Hospital, Kingsbridge Road, Bronx, New York City, came under the supervision of the Deans Committee of the five medical colleges in New York City, conferences have been held each Wednesday afternoon by the Cardiovascular Service. The conference of July 22, 1953, on "Digitalis Intoxication" was recorded and transcribed for publication in this Journal. Participating in that conference were the following: DR. ARTHUR C. DEGRAFF, Senior Consultant in Medicine, DR. BERNARD STRAUS, Director of the Medical Service, DR. LOUIS A. KAPP, Chief of the Cardiovascular Service, DR. WALTER NEWMAN, Assistant Chief of the Cardiovascular Service, DR. LOUIS F. BISHOP, Attending Consultant, DR. O. ALAN ROSE, Attending Consultant, DR. J. B. SCHWEDEL, Attending Consultant, DR. FREDERICK LANDAU, Attending Consultant, DR. HARRY FEIN, Attending Consultant, DR. ARTHUR F. HEYL, guest physician, and resident physicians on the Cardiovascular Service.

DR. KAPP: Today's conference will be on the subject of digitalis intoxication. It is felt that a thorough and frank discussion of the topic might be helpful in prevention of digitalis toxicity or recognition of its early manifestations. Dr. DeGraff will make the introductory remarks.

DR. DEGRAFF: There are a number of important points to bring out in connection with digitalis intoxication. First, digitalis is unique because the range between the therapeutic dose and the toxic dose is very narrow. If the therapeutic dose is doubled toxicity will occur in over 50 per cent of patients. With many other potent drugs the therapeutic dose can be doubled, tripled or even quadrupled without getting into serious difficulties. Therefore, because the therapeutic dose is so close to the toxic dose, much greater care must be exercised in using digitalis than many other drugs. Second, it is necessary quite often to go to the minor toxic point with digitalis to be sure that we have the maximum therapeutic effect. It is important, therefore, to know even the minor toxic symptoms of digitalis poisoning. Third, there may be considerable variation in dose from patient to patient; therefore, we cannot say for every patient that one dose will be a therapeutic dose and another dose a toxic dose. The therapeutic dose and toxic dose have to be determined for each individual.

With the increasing popularity of cardiac glycosides there has been a tendency on the part of some physicians to become careless in the administration of these pure principles. Idiosyncrasy to digitalis is so rare that we should realize that when we have symptoms from digitalis, toxicity is usually the cause. Occasionally we find the patient who becomes nauseated on extremely small doses. Toxicity may be manifested in a number of ways. This will be brought out in the discussion. Gastrointestinal, cardiac, or neurologic manifestations or the development of heart failure may occur. We should include in the discussion what to do when a patient becomes toxic to digitalis, particularly if the toxicity is severe. The doctor should not be afraid to use digitalis because of the narrow range between the therapeutic and the toxic dose. Many physicians give such a small dose that it is practically useless and others resort to drugs other than digitalis even though digitalis may be indicated. We must be sure that the patient has just enough digitalis, that he is neither underdigitalized nor toxic.

I think it might be important to point out

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how toxicity may occur with initial digitalization. Toxicity is apt to occur in using the so-called single digitalizing dose. Although most of the patients who receive the recommended so-called single digitalizing dose are not digitalized, there are some patients who are made toxic. Toxicity may occur by gradually increasing the dose in digitalizing rather than following the usual method of giving the largest dose first and then decreasing doses until the patient is digitalized. Toxicity may also be produced by giving the dose at too frequent intervals so that the full effect of the preceding dose had not yet been obtained. This could occur with a glycoside such as digitoxin where a single dose intravenously will not produce maximum effect for eight hours. This drug certainly should not be given at closer intervals than eight hours. It might also be pointed out that we cannot any longer tell from the color of a tablet whether or not a patient has been receiving digitalis, because tablets now come in all colors—pink, white, green, etc. A patient may become toxic on a maintenance dose of digitalis if the doctor does not realize that there is slow accumulation of digitalis in the body, particularly if digitoxin is used. We may find that the patient gets along perfectly well on a given maintenance dose for a period of several weeks and then develops toxicity, if the same dose is continued, due to slow accumulation of the drug. If the physician does not recognize the early toxic signs a depression of the vomiting mechanism may occur and more serious toxic effects may then follow. We must also remember that the vigorous use of mercurial diuretics may produce toxicity in a patient who is on a maintenance dose of digitalis.

Dr. Kapp: I would like to add a few words with regard to the most common causes of digitalis intoxication. Ignoring early signs or symptoms of digitalis toxicity may be responsible for more severe toxic manifestations. Other causes of toxicity are: administration of digitalis when it is not needed; errors in prescriptions—confusing "q.i.d." and "q.d."; self or uncontrolled medication of digitalis; and absence of the usual gastro-intestinal warning signs of digitalis intoxication, or the presence of other diseases which obscure the clinical evidence of digitalis toxicity. The importance of electrocardiographic examination in the course of digitalization in order to prevent serious cardiac arrhythmias must not be overlooked. We feel that this is especially essential in digitalization of patients with auricular fibrillation, as the presence of extrasystoles might easily be overlooked. Another point which I would like to mention is the danger of using rapid digitalization with large doses, orally, or intravenously, where slower methods of digitalization would have sufficed. Electrolyte imbalance, hypopotassemia or hypercalcemia are additional factors which may influence digitalis toxicity.

We will now proceed with the next phase of our conference—the presentation of illustrative cases of digitalis toxicity.

Dr. March, would you please present the first case.

Dr. March: The patient was a 55 year old white male with a two-year history of hypertensive cardiovascular disease and a one-week history of congestive heart failure. He was admitted with severe left and right-sided failure secondary to hypertensive cardiovascular disease. He was treated with a low salt diet, 2 cc. of Mercuhydrin, and Digoxin, 1.5 mg. initially and then 0.5 mg. every six hours to a total of 5.0 mg. in 48 hours, at which time he developed anorexia and nausea. By this time he had lost 20 pounds and an electrocardiogram revealed auricular fibrillation with complete heart block and a ventricular rate of 60. Digoxin was discontinued and 24 hours later auricular fibrillation was present without heart block. In 48 hours, regular sinus rhythm was present and the patient was placed on Digoxin, 0.5 mg. once daily. He lost 22 pounds in the next 12 days and was discharged in two months.

Dr. Kapp: Dr. DeGraff, would you please comment on the management of this case.

Dr. DeGraff: In the first place, this patient was terribly overtreated. I don't think giving him a salt-free diet, mercurial diuretics and digitalis in large doses, all at the same time, was at all necessary. We would have learned a great deal more about the patient if he had been treated first by bedrest, then digitalized and, if necessary, given a mercurial diuretic. As it turns out, it appears that a mercurial diuretic was not necessary at all.

The second point is that this patient did develop rather severe toxicity. Both the auricular fibrillation and the heart block were signs of digitalis toxicity. Fortunately, Digoxin which is a rapidly dissipated glycoside was given so that toxicity was fairly short. The patient lost all signs of toxicity in 48 hours. If the patient had been on a glycoside which had a long period of dissipation he would have been toxic much longer. Whether or not the rapid loss of weight had anything to do with the rapid development of toxicity is hard to say, but it is not necessary to have a patient lose such a large amount of weight in such a short period of time. I think it should be pointed out that the development of auricular fibrillation in a patient initially having regular sinus rhythm is an important toxic manifestation of digitalis.

DR. KAPP: Would you consider the presence of a complete heart block a contraindication to the use of digitalis?

DR. DEGRAFF: If the heart block is produced by digitalis, I would say yes. If the patient had complete heart block to begin with, and is in congestive heart failure, I would not consider the complete heart block a contraindication to digitalis. I would say that, as a rule, heart block is not a common manifestation of digitalis toxicity.

DR. KAPP: Are there any other questions or comments?

DR. BISHOP: Isn't it rather unusual to develop auricular fibrillation as the initial arrhythmia in digitalis intoxication?

DR. DEGRAFF: No, although it is much less common than ventricular premature contractions.

DR. HEYL: Dr. DeGraff, how often do you see paroxysmal auricular tachycardia as a result of digitalis intoxication?

DR. DEGRAFF: It is possible, I am sure, but must be rare.

DR. HEYL: I published one such case.[1]

DR. KAPP: We will now proceed with the second case.

DR. MARCH: A patient with rheumatic heart disease who had mitral stenosis and aortic insufficiency was treated at home for congestive heart failure with digitoxin, 0.2 mg. twice daily for one week and then 0.2 mg. once daily for one month. At first, he felt better but then observed the recurrence of dyspnea, orthopnea and ankle edema. He was admitted with a diagnosis of rheumatic heart disease and congestive heart failure secondary to digitalis toxicity. On admission he had bigeminal ventricular premature contractions and second degree heart block. With no digitalis, congestive heart failure cleared in two weeks. At first because of ventricular premature contractions he was given Pronestyl and the ventricular premature contractions disappeared in 24 hours. After two weeks, second degree heart block reverted to first degree while under Pronestyl therapy. He was then digitalized with 4.0 mg. Digoxin in three days and placed on maintenance digitalis leaf 0.1 Gm. daily on discharge.

DR. KAPP: Dr. Straus, would you please give us your thoughts on the management of this case.

DR. STRAUS: This patient illustrates some of the objections which have been raised to digitoxin largely in relation to the fact that its dissipation rate is so slow. He received 0.2 mg. of digitoxin twice a day for one week, or 2.8 mg. over a period of seven days, which is not very much higher than the average digitalizing dose of 2.2 mg. noted by DeGraff, Batterman and Rose.[2] But the important thing demonstrated by these studies is that the range of the digitalizing dose for digitoxin is very wide. The range, as these authors found it for the total digitalizing dose, is 0.9 mg. to as high as 4.8 mg. This man presumably received a dose of digitoxin that was toxic for him. We ought to emphasize here that toxicity from any glycoside may produce congestive heart failure as it occurred here. A damaged heart especially is more susceptible to overdosage than is a normal heart, and overdosage with digitoxin presumably threw this man into congestive failure. Stopping administration of the drug is, of course, the first thing to do. In addition, Pronestyl was used in this case to eliminate the ventricular premature beats, with some degree of success. Pronestyl has been successful in correcting various arrhythmias due to digitalis toxicity. It has been stated that ventricular tachycardia due to digitalis toxicity may be favorably influenced by large doses of quinidine. But there are cardiologists who feel that this is somewhat hazardous because of the danger of inducing ventricular fibrillation and

I would think that Pronestyl orally in doses of 0.5 Gm. four times a day or 0.5 Gm. to 1 Gm. intravenously probably would be less dangerous. It is also possible to get a similar effect with potassium chloride in divided oral doses of about 4 Gm. a day. I think potassium chloride is a little more hazardous than Pronestyl.

DR. KAPP: Dr. DeGraff, do you feel that digitalis toxicity may produce myocardial damage?

DR. DEGRAFF: Definite pathologic changes have been demonstrated in the myocardium of animals rendered toxic with digitalis. There is a good possibility that severe or prolonged digitalis toxicity in man may also produce some myocardial damage.

DR. ROSE: I would like to make one comment apropos the use of quinidine in the management of ventricular arrhythmias due to digitalis intoxication. Before the advent of Pronestyl we had success with quinidine in the management of ventricular arrhythmias due to digitalis intoxication. I think the use of this drug should be considered when Pronestyl is unavailable or contraindicated for various reasons.

DR. KAPP: Would you use potassium?

DR. ROSE: Yes, it might be helpful, and it would be indicated in those cases where there is evidence of potassium deficiency.

DR. KAPP: Dr. March, will you please present the next case?

DR. MARCH: This patient, with malignant hypertension, had a sympathectomy on Feb. 18, 1952. On the eleventh postoperative day he developed symptoms of congestive heart failure. Digoxin, 6.75 mg., and 2 cc. Digifolin intramuscularly were given in 48 hours and ventricular tachycardia supervened on March 2, 1952. Digitalis was discontinued and he was then given Pronestyl, 500 mg. every four hours by mouth. On March 3, 1952 his electrocardiogram changed to indicate interference dissociation with a ventricular rate of 110. On March 5, 1952 he had a nodal rhythm with a rate of 96. On March 8, 1952 the patient was found to be azotemic. It was felt that this might be secondary to a low salt syndrome on the basis of a calculated sodium estimated from the chlorides and carbon dioxide. He was therefore given a calculated amount of sodium chloride by Levine tube. At this time his electrocardiogram on the basis of a prolongation of the Q-T interval was interpreted as reflecting hypopotassemia. On March 9, 1952, 6 Gm. potassium chloride were given orally. On March 10, 1952, he received 12.5 Gm. sodium chloride and 4 Gm. potassium chloride intravenously and suddenly expired.

DR. KAPP: Dr. Newman, would you care to comment on the management of this case.

DR. NEWMAN: I think there are several points worthy of comment in this case. First of all, this patient went into cardiac failure for the first time on his eleventh postoperative day. Usually when patients go into cardiac failure for the first time they are gotten out of failure with relative ease as compared with the patient who has been compensated by medical means for a long time and despite this has an exacerbation of his failure. In the light of this, and in view of the arrhythmias which developed after digitalization, I feel that the amount of digitalis given to this patient was excessive. The severe digitalis toxicity manifested by ventricular tachycardia was then treated by discontinuing digitalis and using Pronestyl as a prophylactic measure against the development of ventricular fibrillation. I think the next thing that is worthy of comment is the variety of arrhythmias that this patient demonstrated. He went from a ventricular tachycardia to interference dissociation and then to a nodal rhythm. We can say in general that one can see almost any arrhythmia as a result of digitalis intoxication, and this patient demonstrates at least three different types of arrhythmias which can be attributed to digitalis intoxication. The next error which I think is rather flagrant here does not pertain necessarily to digitalis intoxication. It is the use of a calculated sodium in the presence of azotemia. One cannot calculate sodium on the basis of chlorides and carbon dioxide plus 10 mEq. in the presence of azotemia, because the phosphate and sulfate radicals can no longer be estimated at 10 mEq.; this patient, therefore, may have been given sodium erroneously. The next error that may have been made pertains to the interpretation of the electrocardiogram as being due to hypopotassemia. Prolongation of the Q-T interval may be due to other things besides hypopotassemia; we have here a situation in which a patient was

given potassium without adequate study, and the prolongation of the Q-T interval may very well have been due to Pronestyl in this particular case. There are detectable differences in the prolongation of the Q-T interval due to hypopotassemia as opposed to Pronestyl. Finally, I think the most important error that was committed here was the administration of potassium to this individual in large doses intravenously without adequate chemical control and in the presence of renal insufficiency. Potassium has been shown to be of value, probably through two mechanisms, in the management of arrhythmias from digitalis intoxication. One is an intrinsic depressant effect of potassium on the myocardium so that it is capable of depressing irritable foci. The second mechanism is thought to be related to the observation that digitalis at least in toxic doses is capable of depleting the heart muscle cell of potassium so that the use of potassium in the presence of digitalis intoxication may favorably influence the cellular electrolyte balance and thus the arrhythmias.

DR. KAPP: Dr. Newman, would you advise similar precautions in the use of calcium?

DR. NEWMAN: It has been demonstrated that calcium has a synergistic effect with digitalis and the use of calcium in an already digitalized patient may be hazardous and produce serious toxic reactions.

DR. STRAUS: The point that you are emphasizing, Dr. Newman, is that to give potassium intravenously to an individual with renal damage, without first determining the serum potassium, is extremely hazardous. Serum potassium levels can be readily determined in most hospitals by the use of the flame-photometer. A question that I would like to ask, Dr. Newman, is whether you can relate the quantity of digitalis required to the severity of the heart disease?

DR. NEWMAN: There are too many other factors involved to say that the absolute quantity of digitalis required by a patient is a measure of the severity of his heart disease. However, I would say that the therapeutic range of digitalis tends to narrow as the heart disease progresses. This narrowing is usually due to an increased requirement for digitalis and a decrease in the toxic dose. One finally reaches a point where the toxic dose is lower than the therapeutic dose.

DR. DEGRAFF: We do find as cardiac patients go on with their congestive heart failure that they no longer can tolerate a therapeutic dose but must be given what amounts to a maximum tolerated dose. Many patients in the terminal stages of their heart failure can tolerate less digitalis than they did earlier in their course.

DR. KAPP: Dr. DeGraff, do you recommend using digitalis to toxicity routinely in advanced cases?

DR. DEGRAFF: Only in order to determine whether or not the patient has received the maximum effect from digitalis. There is a considerable variation in the dosage that patients require. We frequently do not know whether a patient has received a therapeutic effect; therefore we may find it necessary to go cautiously beyond what we consider a therapeutic dose up to a minor toxic dose and then drop back to a lower dose when we are sure that that particular patient is getting the maximum therapeutic effect from digitalis.

DR. STRAUS: There has been some trend away from the giving of digitalis either in the form of leaf or glycoside in accordance with body weight. I know that a number of cardiologists feel that the old Eggleston formula is unsatisfactory and should be discarded. Many cardiologists are not administering digitalis according to body weight. What is your feeling, Dr. DeGraff? Can you relate the total dosage of the glycoside to the true body weight?

DR. DEGRAFF: The weight only gives you a rough approximation of the dose required. The greatest value of the Eggleston dosage method is that it begins with a large fraction of the total dose first and then smaller fractions till the patient is digitalized. Prior to the time of Eggleston the custom was to give a small dose of digitalis, the next day a little larger dose and the next day a still larger dose until suddenly the patient became toxic. I think the greatest lesson learned from the Eggleston technic was that it taught us to give digitalis as one would do a chemical titration. In that way severe toxicity could be avoided.

DR. KAPP: Dr. DeGraff, is the age of the patient a factor in digitalis dosage?

DR. DEGRAFF: I think older people in general require smaller doses of digitalis than younger people. However, the dose must be considered on an individual basis.

DR. KAPP: If there are no further questions we will then proceed with the final case.

DR. MARCH: A 55 year old colored male was admitted with a six-year history of hypertensive cardiovascular disease and a five-year history of congestive heart failure. He was on a regimen of digitoxin, 0.2 mg., daily for one year, and on a low salt diet and occasional mercurials for five years. He was admitted here in 1951 with symptoms and signs of congestive heart failure. Examination of the heart revealed a regular sinus rhythm, frequent ventricular premature contractions and runs of ventricular tachycardia. The electrocardiogram disclosed first degree heart block, left bundle branch block, frequent premature ventricular contractions and runs of ventricular tachycardia. An enlarged heart, particularly the left ventricle, and evidence of pulmonary engorgement was seen on x-ray film of the chest.

On admission to the hospital, digitalis was discontinued. With a low salt diet, bedrest and occasional mercurials, the ventricular premature contractions disappeared, although first degree heart block and left bundle branch block persisted. Eleven pounds were lost over a period of two weeks with some residual congestive heart failure. He was then given 5.5 mg. of Digoxin in three days and placed on 0.75 mg. as a maintenance dose. After three weeks on this dosage, complete heart block appeared. Digoxin was discontinued and in four days, first degree heart block reappeared. Two weeks later the patient was given 5.0 mg. of Digoxin in three days without toxicity and then 0.5 mg. daily. In five weeks there were frequent and multifocal premature ventricular contractions. He was therefore given 0.5 Gm. Pronestyl four times daily, and the premature ventricular contractions disappeared. Ten days later, Pronestyl was stopped and Digoxin continued. Within 72 hours, ventricular premature contractions began and digitalis was discontinued. In 48 hours he developed evidences of congestive heart failure, marked increase in ventricular premature contractions and runs of ventricular tachycardia. He was therefore returned to 0.5 Gm. Pronestyl four times daily and 5 mg. Digoxin in the next three days, and thereafter placed on a daily maintenance of 0.5 mg. Digoxin with disappearance of congestive heart failure and premature ventricular contractions. He was then discharged from the hospital. He did well for approximately three months. Two weeks prior to his second admission he discontinued Pronestyl. Two days later he noted dyspnea and palpitation. These symptoms persisted and he was therefore readmitted. At that time there was evidence of mild congestive heart failure with ventricular premature contractions and runs of ventricular tachycardia. He was given Digoxin, 0.5 mg. daily, and Pronestyl 0.5 Gm. four times daily. The premature contractions and congestive heart failure disappeared.

DR. KAPP: Dr. Rose, would you please analyze the therapeutic problems in this case?

DR. ROSE: This patient illustrates a number of very interesting features relative to digitalis toxicity. The first point that I would like to make is that the patient had been on the same dose of digitoxin for one year. This would ordinarily be long enough to be reasonably certain that the daily digitalis dose was not a toxic one. This raises the question whether the findings of ventricular premature contractions and the first degree block were due to underlying heart disease or digitalis toxicity. It illustrates the important point that when a patient is first seen and there is a reasonable doubt whether digitalis toxicity is present, digitalis administration should be stopped. Though it had appeared unlikely that digitalis toxicity was present in the patient under discussion, the discontinuance of the drug for a period was apparently, at least in part, responsible for the clearing of his failure. Under these circumstances particularly, when one is able to observe the patient frequently, it is always advisable to discontinue digitalis temporarily and use other supportive measures.

The second point which this patient demonstrates is one which Dr. DeGraff has mentioned already: as heart disease progresses, a daily maintenance dose of digitalis which was originally a therapeutic dose may become a toxic dose; apparently this occurred in the case under discussion. Patients under these circumstances usually require reduced dosages of digitalis and the institution of mercurial therapy. We have recently, and with considerable caution, been using Pronestyl for the treatment of multiple ventricular premature contractions due to digitalis effect in the hope of maintaining the therapeutic effect of a dose of digitalis which would ordinarily produce ventricular premature contractions. When

this dose is used in combination with Pronestyl, digitalis is not infrequently tolerated without the appearance of ventricular premature contractions. This raises the interesting question whether the appearance of ventricular premature contractions in such a patient is really a manifestation of digitalis intoxication or whether congestive failure or some other factor may be responsible for increased ventricular irritability and the occurrence of ectopic beats. It is notable in this and other similar cases that patients can be maintained on doses of Digoxin which previously produced ventricular premature contractions and that congestive failure may subside when Pronestyl is added and premature contractions controlled. Premature ventricular contractions under these circumstances do not appear to be an evidence of digitalis toxicity but may be precipitated by myocardial hyperirritability. At least in some cases, if you can control the hyperirritability factor, you can maintain the patient on a good therapeutic dose of digitalis without risking any other evidence of toxicity. If this patient had had other evidences of toxicity, such as severe anorexia and nausea, the continued use of digitalis with Pronestyl would not have been a safe procedure. We must remember that Pronestyl, like quinidine, is a myocardial depressant and if the myocardium is already depressed by the presence of digitalis toxicity, further depression with quinidine or quinidine-like drugs is probably hazardous and might increase the degree of failure.

I would like to say a word about the use of Pronestyl in general, and to introduce a note of caution. Pronestyl is a new drug and has not been used for a long enough period of time for us to be fully cognizant of its toxicity and possibly of all its toxic manifestations. Already ventricular fibrillation has been reported as being due to Pronestyl administration when it was given parenterally. Agranulocytosis and drug fever have also been reported. I do not think that we can say that the use of Pronestyl indiscriminately is advisable under any circumstances, and patients who are receiving Pronestyl, particularly under these somewhat precarious conditions, should be observed very carefully with frequent electrocardiograms to determine what effects are being achieved. Blood studies should also be repeatedly made.

DR. DEGRAFF: How important do you consider the electrocardiogram in determining digitalis toxicity?

DR. ROSE: The important evidences of digitalis toxicity on the electrocardiogram are evidences of arrhythmias due to myocardial hyperirritability. The appearance of ventricular premature contractions and particularly runs of ventricular tachycardia or coupling are the most striking electrocardiographic evidences of digitalis toxicity. Changes due to digitalis are expected in the S-T segment and the T wave. These are normal changes on the electrocardiogram, due to digitalis; the changes are extremely variable depending upon the individual and are not alone evidence of toxicity. I think the answer to your question is that the arrhythmias are the things we watch out for, particularly the presence of ventricular premature contractions which can often only be detected electrocardiographically especially when auricular fibrillation is present.

DR. NEWMAN: I would like to add that it can sometimes be very difficult to detect clinically a complete heart block when the ventricular rate is about 60, as sometimes happens, and under those circumstances the electrocardiogram may give you the only clue to the existence of a severe form of digitalis intoxication.

DR. ROSE: I forgot to mention conduction defects. These may certainly be important evidence of digitalis toxicity.

DR. KAPP: Dr. Rose, in case of auricular fibrillation with a ventricular rate of 40 under digitalis administration, would you consider this a manifestation of digitalis intoxication?

DR. ROSE: Not necessarily. Frequently patients with considerable cardiac enlargement have a better cardiac function with ventricular rates as slow as 40. Other evidences of digitalis toxicity should be looked for, and the ventricular rate should not be taken alone as an indication of toxicity.

DR. KAPP: But it has been pointed out frequently that the development of heart block is quite a serious indication of digitalis toxicity. If a patient with auricular fibrillation suddenly

develops a slow, regular rhythm while on digitalis, a block may have occurred.

DR. ROSE: Complete heart block developing during the administration of digitalis would be an indication to discontinue the digitalis therapy. If however a block is present in a patient who is in failure and not digitalized, the block is not, per se, a contraindication to the use of digitalis.

DR. KAPP: In the presence of sinus rhythm it is relatively easy to determine when complete heart block has occurred; however, with auricular fibrillation it is not simple to determine the presence of complete heart block so that if such a patient should develop a ventricular rate of 40 I should think that this would be an indication to proceed cautiously with further digitalis.

DR. ROSE: I agree with you that one should proceed cautiously when the ventricular rate drops to this range since digitalis intoxication may not be far off with a ventricular rate of 40 in a patient with auricular fibrillation. However, even with a ventricular rate of 40 one can usually detect the irregularity of auricular fibrillation to indicate that complete heart block is not present. Fibrillation at a rate of 40 would not be an indication, per se, to discontinue digitalis.

DR. KAPP: There is another form of block, so-called interference dissociation, which is a very frequent sign of digitalis toxicity. In this form very rapid ventricular rates occur, either of idioventricular or nodal origin, with an occasional beat due to a sino-auricular stimulus.

Are there any other comments on this fourth case? If not, we will then proceed with a number of questions submitted by the residents and other members of the staff.

Dr. Bishop, can diuretics aggravate or perpetuate digitalis intoxication, and what is the mechanism?

DR. BISHOP: I think we have had some comment on that already. When a patient is on digitalis and a large diuresis occurs, it is quite common for the patient to become toxic. You must be extremely careful, therefore, in using mercurials in patients who are on digitalis therapy.

DR. KAPP: Any further discussion?

DR. SCHWEDEL: Ordinarily a cardiac patient can excrete almost as much potassium as he ingests. He may excrete 40 to 50 mEq. potassium daily, but after a mercurial he may double this excretion. This results in a real potassium depletion and arrhythmias. Such arrhythmias, produced as a result of digitalis intoxication plus mercurials often may be controlled by giving an equivalent amount of potassium by mouth.

DR. STRAUS: You feel, then, that it is a result of both the mobilization of digitalis by the diuretic and hypopotassemia.

DR. SCHWEDEL: Yes.

DR. KAPP: Any other questions?

DR. LANDAU: I want to ask a question. It has been advised that patients who have digitalis intoxication and are given mercurial diuretics routinely every five to seven days should be given a large glass of orange juice every day in order to maintain them in a fairly good potassium balance. I would like to ask Dr. Schwedel if this simple method is sufficient in most cases.

DR. SCHWEDEL: Yes, it is.

DR. KAPP: Dr. Newman, would you permit patients with renal insufficiency to drink orange juice?

DR. NEWMAN: I don't think the amount of potassium that would be ingested in a glass of orange juice would be deleterious to a patient with renal insufficiency.

DR. KAPP: It has been pointed out that auricular fibrillation can be a manifestation of digitalis intoxication. I would like to ask Dr. Landau if he has seen auricular flutter as a manifestation of digitalis intoxication.

DR. LANDAU: I cannot remember ever having seen one but I have seen it described on several occasions in the literature.[3, 4]

DR. KAPP: Dr. Fein, what precautions would you advise in the treatment of a case of acute myocardial infarction who is in congestive heart failure?

DR. FEIN: In an instance of acute myocardial infarction the usual precaution is slow and more careful digitalization than one would usually undertake if there were no myocardial infarction. Digitalis intoxication should be

avoided during the acute phase of a myocardial infarction.

DR. KAPP: Would you ever use parenteral digitalis in a case of myocardial infarction with acute congestive failure?

DR. FEIN: I would be loathe to use parenteral digitalis routinely in the case of myocardial infarction with congestive heart failure. However, I would not say that I would never use it, rather reserving it for those instances of very rapidly and acutely developing congestive heart failure where quick action is necessary to be life saving.

DR. ROSE: If a patient develops rapid auricular fibrillation and is rapidly going into failure, I do not feel that the presence of acute myocardial infarction would contraindicate the use of an intravenous ouabain or some other rapidly acting glycoside parenterally. It would probably then be used as a life-saving measure.

DR. KAPP: You would then make exceptions?

DR. ROSE: Yes, I would.

DR. DEGRAFF: I think one of the important problems to face in a digitalized patient with a myocardial infarction is the occurrence of ventricular premature contractions. You cannot tell whether they are due to the infarct or to the digitalis toxicity. The size of dose does not always help us in the differentiation. The patient may be susceptible to digitalis and even though the dose is low the premature contractions may then be due to digitalis. I think the wise thing to do would be to stop the digitalis if you are in doubt.

DR. KAPP: There is some question whether the nausea and vomiting of digitalis intoxication are of central or local origin. Dr. DeGraff, what is your opinion?

DR. DEGRAFF: I think that the evidence at present would indicate that it is both. Occasionally a patient will take an extremely small dose orally and develop gastrointestinal symptoms. Such a patient may be able to tolerate a much larger dose intravenously. I can recall a patient with auricular fibrillation in whom all the glycosides had been tried orally; with none of them could a dose be reached that would slow the ventricular rate. When the medication was given intravenously this patient enjoyed a very good therapeutic result without any nausea or vomiting or any other toxic manifestations.

DR. STRAUS: Generally speaking, though, the local toxic effects on the gastrointestinal tract occur earlier than the central effects which are usually manifested later in the course of digitalization. Isn't that true?

DR. DEGRAFF: There are two local effects. (1) The irritant effect of the drug itself which is rather rare. It is only when a large amount of the tincture or several tablets of the powdered leaf are given at the same time that local irritant effect may be produced. It is almost an immediate effect of the drug. (2) The effect of the drug after it is in the gastrointestinal tract for some time. The dose to produce this effect is usually somewhat lower than the dose producing the central effect. There is, however, considerable variation from patient to patient. In some the dose necessary to produce the local and central effects is about the same. In others, there is quite a spread.

DR. KAPP: Dr. Bishop, how would you handle a patient, whom you see for the first time, who is in congestive heart failure and has been treated with digitalis, dosage and duration unknown, and who has ventricular premature contractions some of which are bigeminal.

DR. BISHOP: The possibility exists that these bigeminal ventricular premature contractions are a toxic effect of digitalis. At the same time we are faced with the fact that bigeminal ventricular premature contractions can be a manifestation of congestive heart failure. We are, therefore, at a loss to know which of the two possibilities are operating. I would wait a while and see how the patient got along without digitalis, provided the congestive heart failure was not too severe and going into an irreversible stage. I think there is often a tendency to treat failure too quickly; if you wait a while and have the patient under observation it may not be necessary to start digitalis immediately. But if after a period of time it became evident that this was not the case, that the premature beats did not represent digitalis intoxication and that the bigem-

inal rhythm was a manifestation of failure, then I think you would be justified in going ahead and digitalizing this patient.

DR. KAPP: Would you use a mercurial in such a case?

DR. BISHOP: Well, I'm not so much in favor of using mercurials right away. Again I would be inclined to wait and use digitalis first. I know that some men use mercurials right away in the management of congestive heart failure. But that is another subject.

DR. KAPP: In other words, if I understand you correctly, you would first use bedrest and a low salt diet and then, if the failure did not improve or gradually became worse, you would slowly proceed with digitalis watching the effect on the extrasystoles. If they increase then you would stop the digitalis. If they decrease, you would assume they were due to congestive heart failure.

RESIDENT: If a patient is kept on a mildly toxic dose of digitalis, is this dangerous?

DR. DEGRAFF: Yes. You may depress some of the early toxic manifestations and your first toxic manifestation under such circumstances may be a ventricular tachycardia. One must know what is the earliest toxic manifestation of digitalis. This usually is a loss of appetite. It is this symptom that the physician often misses. It comes before nausea. Very often even before that, if you are watching the patient very carefully, you may notice a change in personality. They may become morose or melancholy where before they were cheerful.

DR. STRAUS: The question whether a patient should be routinely digitalized to toxicity deserves a little further discussion. There are those who advocate digitalizing to toxicity in all cases on the theory that it is impossible to know when there is full digitalization unless toxic manifestations appear. I think, myself, that is an objectionable point of view. My major objection to the establishment of that policy as a routine is that it is often unnecessary. There are a good many individuals who are in mild failure in whom one can get a perfectly adequate therapeutic result without any apparent toxicity. I see no point in making such a patient toxic. Then there is another type of case in which the only manifestation of failure is paroxysmal nocturnal dyspnea. That type of case can very often be controlled on minimal doses of digitalis without any manifestations of toxicity. I think it would be unwise to adhere to a fixed routine and continue an individual like that on a dosage which will lead to toxicity. That is my own point of view. I would like to hear from others.

DR. ROSE: I would, in general, agree and I would like to assure Dr. Straus that on this service we do not invariably digitalize patients to toxicity. In those patients whose cardiac reserve is very much diminished and who have an extremely narrow therapeutic range, it is frequently necessary to digitalize to the point of toxicity in order to be certain that you are in the therapeutic range. If the patient is on the other side of the scale, is in failure for the first or second time and has a relatively good cardiac reserve, one can usually get into the therapeutic range without producing toxicity. Most patients fall into this group with a fair reserve in which digitalization to toxicity is not necessary.

DR. DEGRAFF: I think there is one point that should be made about digitalis at this time, and that is that digitalis is not effective if its concentration in the body is below a certain point. Very small doses of digitalis will have no effect whatsoever on the patient. We must get a certain minimal concentration in the patient's body in order to get an effect. In giving digitalis to a patient we frequently don't know whether that patient is getting a maximum therapeutic effect. Therefore we cautiously raise the dose in the hope of getting a better therapeutic effect. Now if in doing so we come to a point of minor toxicity then we know we have exhausted the therapeutic possibilities of the drug and we must use something else. In this case we drop back to a dose which is actually the maximum tolerated dose and then go on with other forms of therapy.

DR. NEWMAN: I think there is one other situation where one has to take digitalis to a minor toxic dose; namely, when one is trying to convert auricular flutter to either fibrillation or sinus rhythm. It is also important to state that when the physician has decided to take a patient to minor toxicity, he should be in a position to observe the patient carefully and also take frequent electrocardiograms which may be limited to long strips of one lead for purposes of evaluating the rhythm.

DR. KAPP: Dr. DeGraff, it has been stated that since the introduction of pure glycosides, diarrhea is a rare manifestation of digitalis intoxication.

DR. DEGRAFF: Actually, diarrhea was relatively infrequent even with the powdered leaf many years before we used the glycosides. The only real difference with the glycosides is in the duration of the toxicity. It may be generally stated that the longer the latent period, the more persistent the toxic symptoms. On the other hand, the shorter the latent period, the shorter the period of toxicity.

DR. KAPP: Dr. Landau, can ephedrine or epinephrine precipitate toxic manifestations in patients treated with digitalis?

DR. LANDAU: I have had no personal experience with this.

DR. FEIN: I too have had no personal experience with this, but theoretically these drugs can enhance the toxicity of digitalis, at least in connection with the arrhythmias.

DR. DEGRAFF: You would certainly not give epinephrine or ephedrine to a patient who was toxic from digitalis.

DR. ROSE: These drugs might bring out a latent irritability of the myocardium from digitalis.

DR. KAPP: In case of intolerance to digitalis with soxic manifestations, should gitalin betried?

DR. ROSE: If, because of very advanced heart disease, a patient cannot be adequately digitalized without toxicity using other preparations, he will probably not be able to tolerate gitalin either. However, if a patient has a therapeutic range which is extremely narrow and you cannot get into this range using other preparations without producing toxicity, gitalin may be effective in accomplishing this. Gitalin is presently being used chiefly for this purpose. However, it is also, by virtue of its wider therapeutic range, a safer drug to use for rapid digitalization.[5] A good therapeutic effect can usually be achieved long before toxicity is reached.

DR. KAPP: Can carotid sinus hypersensitivity be aggravated by digitalis toxicity?

DR. DEGRAFF: It certainly can. It will vary, of course, from patient to patient.

DR. KAPP: Dr. Schwedel, can you comment on the various neurologic manifestations of digitalis intoxication.

DR. SCHWEDEL: In a recent survey Dr. Batterman[6] has gathered together a large series of patients who have developed neurologic manifestations of digitalis intoxication. However, these are relatively rare compared with the gastrointestinal and rhythmic manifestations of digitalis intoxication. The vagal disturbances are much more common.

DR. STRAUS: Convulsions have also been observed with digitalis toxicity without the Adams-Stokes syndrome.

DR. KAPP: In a case of ventricular tachycardia in a patient not on digitalis who then develops congestive heart failure, would you use digitalis?

DR. DEGRAFF: I would prefer to treat the ventricular tachycardia first with Pronestyl.

RESIDENT: In patients with cor pulmonale the cardiac rate is often rapid in the absence of failure and a therapeutic effect may be difficult to evaluate. What are the dangers of digitalizing to toxicity with these patients?

DR. DEGRAFF: In treating cor pulmonale, digitalization rapidly is apt to produce an increase in the pulmonic arterial pressure, in which case the patient becomes worse. On the other hand, if digitalization is done slowly eventually a good therapeutic effect from digitalis is obtained. As far as the toxic manifestations are concerned, I think that one should be extremely careful not to give anywhere near the toxic dose in these cases.

DR. NEWMAN: At one time it was felt that digitalis was not efficacious in the management of congestive heart failure in cor pulmonale.

DR. LANDAU: There is one controversial question which I wish Dr. DeGraff would discuss just as a matter of record. If a patient has become toxic to digitalis, is it possible that the heart will show irreversible evidence pathologically that he has been toxic before?

DR. DEGRAFF: Usually no, but occasionally yes. In one patient who became toxic on digitoxin, T-wave changes persisted for a month or more after digitalis was stopped. As mentioned before, pathologists have demonstrated microscopic changes in the heart muscle of animals poisoned by digitalis. This probably also occurs in man in cases of severe or prolonged toxicity. We do know also that congestive heart failure can be precipitated by digitalis and relieved by stopping digitalis.

This would suggest some adverse effect on the myocardium from toxic doses of digitalis.

RESIDENT: Does one see allergy to digitalis?

DR. DEGRAFF: There have been reports of allergy, but they are very rare.

DR. KAPP: Gentlemen, in closing I would like to say that at this conference we have made an attempt to go into some of the essential phases of digitalis intoxication. We do not claim to have covered this topic completely, but we have brought out some important points. I will now ask Dr. DeGraff to give us a summary of the discussion of this conference.

SUMMARY

The major points that have been brought out in this conference on digitalis intoxication are the following:

I. Digitalis intoxication is quite common, particularly since the potent cardiac glycosides have come into general use.

II. The main reasons for the occurrence of toxicity are: (a) narrow therapeutic range of digitalis; (b) lack of appreciation of early toxic signs and symptoms; (c) belief that all patients require the same digitalizing and maintenance dose, thus disregarding evidence that there is a wide dosage range from patient to patient; (d) the use of a glycoside (such as digitoxin) with a long latent period and a long period of dissipation; lack of appreciation of these properties of this glycoside may result in toxicity when divided doses are given at too short intervals in initial digitalization, or too high a maintenance dose is used causing accumulation later.

III. Digitalis intoxication may be indicated as follows: (a) gastrointestinal symptoms due both to local and central effects; (b) central nervous manifestations; (c) effect on the heart itself, such as abnormal rhythms, the most serious of which is ventricular tachycardia; also, there is some evidence that damage to heart muscle may result and heart failure may be induced by digitalis toxicity. Auricular fibrillation may be a sign of digitalis toxicity in a patient who has previously had a regular heart rhythm.

IV. Idiosyncrasy to digitalis may occur but is rare.

V. The treatment of digitalis toxicity consists of the following measures: (a) stop all digitalis medication if toxicity is suspected; (b) treat ventricular tachycardia induced by digitalis by procaine amide; it is to be emphasized, however, that this drug must be used with great care since it can of itself produce serious toxic effects; (c) cases of digitalis intoxication associated with hypopotassemia may be helped by the administration of potassium.

REFERENCES

1. HEYL, A. F.: Auricular paroxysmal tachycardia caused by digitalis. Ann. Int. Med. **5:** 858, 1932.
2. DEGRAFF, A. C., BATTERMAN, R. C., AND ROSE, O. A.: An evaluation of digitoxin for initial digitalization of the patient with congestive heart failure. J. A. M. A. **138:** 475, 1948.
3. COLE, S. L.: Digitalis intoxication. Am. Heart J. **39:** 902, 1950.
4. HERRMANN, G. R., DECHERD, G. M., JR., AND MCKINLEY, W. F.: Digitalis poisoning. J. A. M. A. **126:** 760, 1944.
5. BATTERMAN, R. C., DEGRAFF, A. C., AND ROSE, O. A.: The therapeutic range of gitalin (amorphous) compared with other digitalis preparations. Circulation **5:** 201, 1952.
6. —, AND GUTNER, LEONARD, B.: Hitherto undescribed neurological manifestations of digitalis toxicity. Am. Heart J. **36:** 582, 1948.

CLINICAL PROGRESS

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The Clinical Value of Phonocardiography

By HOWARD B. SPRAGUE, M.D., WITH THE COLLABORATION OF PATRICK A. ONGLEY, M.D.

AUSCULTATION of the heart is an art in which the conclusions of the observer depend upon acuity of hearing, sense of timing, and appreciation of tonal quality of complex transient noises. These noises are often near the lower limit of audibility in respect to intensity and also frequency. Indeed, the experienced listener utilizes the tactile sensation of the ear drum, below the auditory level, in interpreting such signs as third heart sounds and gallop rhythms.

It is desirable to capture and record graphically data on rapidly recurring transient sounds in order to submit them to analysis free from the subjective distortion of hearing. In this connection it should be remembered that the trained ear has the advantage of great sensitivity to the higher pitches of the sounds useful in diagnosis and also it can automatically reject artefacts such as amplifier hums, muscle sounds, and other noises not produced by the heart which might appear as valid vibrations in a phonocardiogram. The warning must be issued, therefore, that phonocardiography is only an additional aid in a small group of cases in which the ear has some limitations, and then only when there is an appreciation of the inherent technical pitfalls in the method.

Phonocardiography has been retarded for several reasons. The major technical advance had to await the development of electronic amplification in which the amplifier output was free from ground noise; in other words, a record had to be produced in which the baseline could be depended upon not to contain oscillations produced in the instrument. A crude recording which I made 25 years ago (fig. 1) illustrates the 60 cycle alternating current in the baseline which vitiates any interpretation of murmurs. A second example (fig. 2) shows modern electronic recording in which one can identify the components of the normal first, second, and third heart sounds.

Richard Cabot was interested in this field over 25 years ago, and his clinical descriptions in hospital records of what he heard in the heart were illustrated with drawings of his auscultatory findings. Figure 3 shows his impression of the sounds he heard in a phonograph record, which he made in 1926, of a patient with mitral stenosis. A note from him of this period shows the problems of a heart sound recorder: "In the record of this last patient and of the previous one there is some extraneous noise, due to a snowstorm which was raging outside the room where we worked."

Another factor affecting the development of

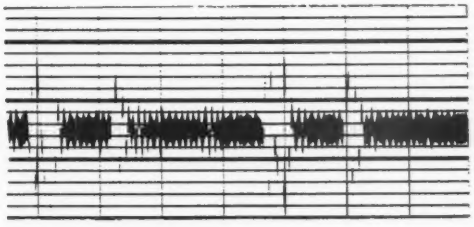

FIG. 1. Phonocardiogram recorded with original Einthoven string galvanometer at Massachusetts General Hospital. First and second sounds can be distinguished, but alternating current artefact in the baseline makes it impossible to record murmurs satisfactorily.

From the Massachusetts General Hospital, Boston, Mass.

Dr. Ongley is a Trainee Fellow, National Heart Institute.

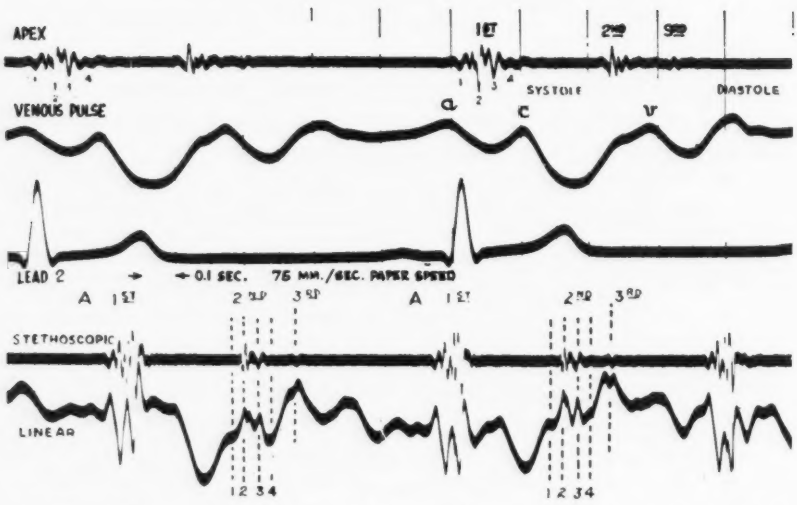

FIG. 2. (From Rappaport and Sprague.[2b]) The normal heart sounds in the stethoscopic phonocardiogram, showing the components of the first and second heart sounds as related to the jugular phlebogram and the electrocardiogram (upper record) and the apex linear cardiogram (lower record).

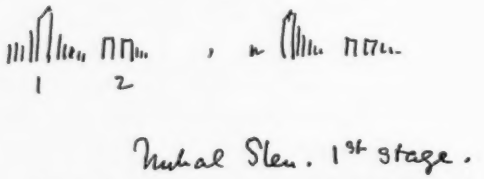

FIG. 3. Sketches and handwriting of Dr. Richard Cabot illustrating the first stage of mitral stenosis. The drawing on the left shows a presystolic murmur, loud first sound, a decrescendo systolic murmur, second sound with either an opening snap of the mitral valve or third sound followed by a short murmur. On the right are the same features except for the absence of the presystolic phase of the diastolic murmur. The mark following the comma between the two sketches is the word "or."

phonocardiography has been failure to recognize the necessity for recording heart sounds with more than one type of microphone and with two different types of stethoscope chest pieces, the open bell and the diaphragm. The clinical importance of the use of these two chest pieces was noted in 1926.[1]

One might imagine that it would be desirable to photograph the jumble of frequencies comprising a heart sound cycle with a microphone which would respond to all frequencies in a linear fashion. This is not practical since the linear displacement of the galvanometer beam produced by the apex beat would be several meters on the same scale of amplification which would move the beam only 1 mm. in recording a soft aortic diastolic murmur. Therefore, the linear microphone is used only to record such gross mechanical movements as those of the chest wall or of the neck veins or of peripheral arteries as reference tracings.[2]

The second type of microphone, the stethoscopic, is so controlled, electronically, that it records those vibrations delivered to the ear by an average stethoscope. Such a record presents the pattern of sound which does not emphasize the higher frequencies to which the ear is peculiarly alert and allows analysis of the lower frequencies which may not always be audible.

The logarithmic, or high frequency, microphone records graphically the sounds and murmurs in a manner comparable to the way in which the brain interprets them since, like the human ear, its distortion is of the type which emphasizes the high frequency, low energy vibrations at the expense of the low frequency, high energy components (fig. 4).

In addition to these three microphones, it is possible to alter the chestpiece as the physician

d es in clinical auscultation, namely, by changi g to open bells of different diameters and diap ragms (Bowles type) of differing thicknesses. C pen bells transmit all frequencies with large b lls emphasizing lower tones, while diap ragms damp out mechanically these lower t nes, permitting the higher notes to appear u masked by them. A diaphragm about twice the usual thickness of 0.015 inch (0.035 inch), will often brilliantly reveal a high pitched murmur. Its use permits high electrical amplification without causing the heart sounds to become loud and booming and thus masking the murmur as in the fatiguing effect on the ear when over-all amplification is increased.

One other feature of phonocardiography must be accepted, and that is the necessity for recording simultaneous reference tracings of cardiac and vascular sounds with which to relate the sounds of the heart. For the timing of systolic activity the electrocardiogram is satisfactory, but for diastolic events the cervical phlebogram and the apex cardiogram are valuable.

To one who is interested in the intricacies of phonocardiography, the recording of all sorts of heart sounds and murmurs is useful in the collection of a permanent portrait gallery of what has been a series of ephemeral auditory impressions. The actual contribution of these portraits toward the understanding of what is going on in the heart is another question. It is to this area that I wish to confine the illustrations of the clinical value of the method.

The recent impressive development of cardiovascular surgery has made accurate diagnosis of congenital defects and acquired valvular lesions of more than academic interest. Cardiac catheterization and angiocardiography have fostered diagnostic humility in the clinician, as has the ability of the surgeon to describe the mechanical activity of the mitral valve which he is actually palpating at operation. However, the time has not come to discard the stethoscope nor to substitute for it the phonocardiograph.

Phonocardiography, however, has shown us, for example, that the normal first heart sound has four components in addition to the auricular sound,[3] that the second heart sound also has four components,[2, 4] and that the third heart sound is truly a manifestation of the rapid inflow stage of the ventricles.[2] It has also been useful in the timing of sounds and murmurs as in loud auricular sounds (fig. 5*a* and 5*b*) confused with first and second sounds, in defining systolic clicks (fig. 6), and even in explaining blowing systolic-diastolic murmurs in children thought incorrectly to be due to patent ductus arteriosus (Fig. 7).[5]

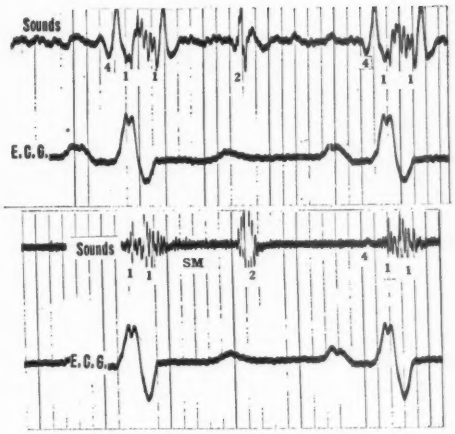

FIG. 4. The upper tracing recorded stethoscopically at the apex shows a widely split first heart sound preceded by a high intensity, low frequency auricular sound. In the lower tracing, recorded logarithmically, the split first sound is clearly seen but the auricular sound (4) appears as a low intensity wave preceding the split first sound. In addition, there are low intensity systolic and diastolic murmurs. The high frequency components of the sounds and murmurs are revealed by the logarithmic recording.

The confusing splitting of sounds is readily interpreted from phonocardiograms (fig. 8). By this method one may demonstrate the presence of murmurs which have been inaudible because of the masking effect of preceding loud sounds or murmurs (fig. 9), and the hiding of heart sounds in loud murmurs (fig. 10). Such has been the case in both the apical and basal areas.

In mitral stenosis it is possible to differentiate the opening snap (fourth component of the second sound) of the mitral valve from the third heart sound and to determine whether or not a short murmur is present after the

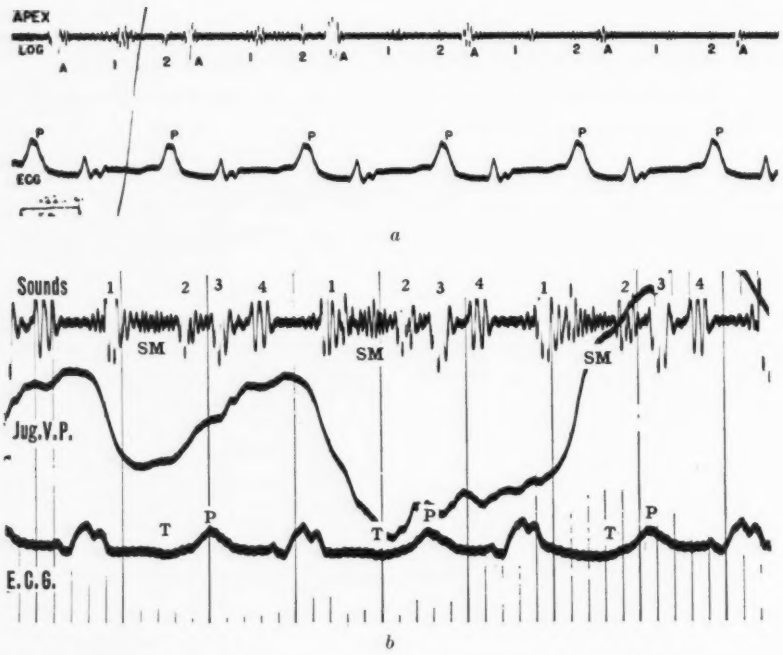

FIG. 5*a*. Logarithmic record at apex of a patient with congenital heart disease, cyanotic type. First sound was described as loud on auscultation; phonocardiogram reveals a faint first sound and a loud auricular sound, which bears constant relationship to the wide, tall, and notched P of the electrocardiogram.

b. Logarithmic record at the apex of a 20 year old white male diagnosed "myocarditis" following an upper respiratory infection. Four heart sounds are shown in the presence of left bundle branch block. The first sound is of normal intensity and is followed by a systolic murmur (SM). The second and third sounds are followed by a loud auricular sound (4).

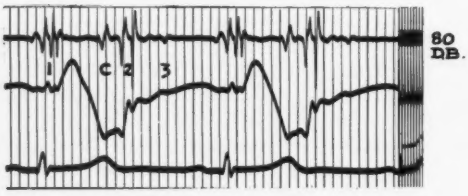

FIG. 6. Systolic click at apex. Stethoscopic (upper), and linear (middle) phonocardiogram, recorded with lead II of the electrocardiogram. (Standardization tone of 80 decibels shown at the right.) A systolic click (c) and 3rd sound are demonstrated.

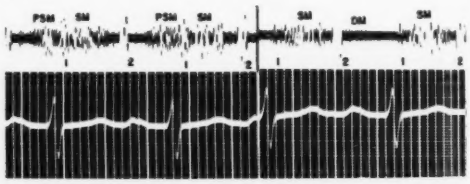

FIG. 7. Logarithmic phonocardiograms (apex, left, and pulmonic area, right) with simultaneous electrocardiograms, lead II of 7 year old girl. The rather unusual blowing presystolic and systolic murmurs were thought clinically to be the continuous murmur of a patent ductus, but the phonocardiogram showed their relationship to the first, rather than the second, sound.

third sound (figs. 11, 12). Also it has defined true mitral stenosis, in which the presystolic murmur always starts before the Q wave of the electrocardiogram, from pseudo mitral stenosis due to modified first heart sounds;[6] and it has shown the delay of the first heart sound, relative to the electrocardiogram, in this condition.[7, 8]

Phonocardiography has not been superior to auscultation in the diagnosis of mitral regurgi-

tion combined with mitral stenosis. At operation a regurgitant stream through the valve has been felt by the surgeon's finger in the left auricle when no systolic murmur has been audible or recordable.

Phonocardiography has shown, however, that the Austin Flint murmur may be indistinguishable from that of mitral stenosis when aortic regurgitation is present and the mitral valve normal at autopsy.[9] The loud first sound at the apex, the sharp opening snap of the mitral valve, and the accentuated pulmonic second sound are the diagnostic points in organic mitral stenosis.

In rare cases tricuspid regurgitation may be shown by systolic vibrations in the jugular veins (fig. 13).

Fifty years ago the clinical observation was made that, in pulmonary stenosis, the first sound over the pulmonary artery was sharp

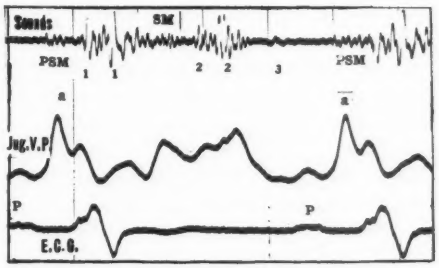

FIG. 8. Logarithmic phonocardiogram recorded at the apex of a 54 year old white male with the clinical diagnosis of "idiopathic cardiac hypertrophy." Bundle branch block is present in the electrocardiogram. There are widely split first and second heart sounds and a third sound. There are also systolic and presystolic murmurs. The latter was thought to be due to the high energy of auricular contraction which was demonstrated by stethoscopic recording in the same area. The jugular pulse also shows a high "a" wave.

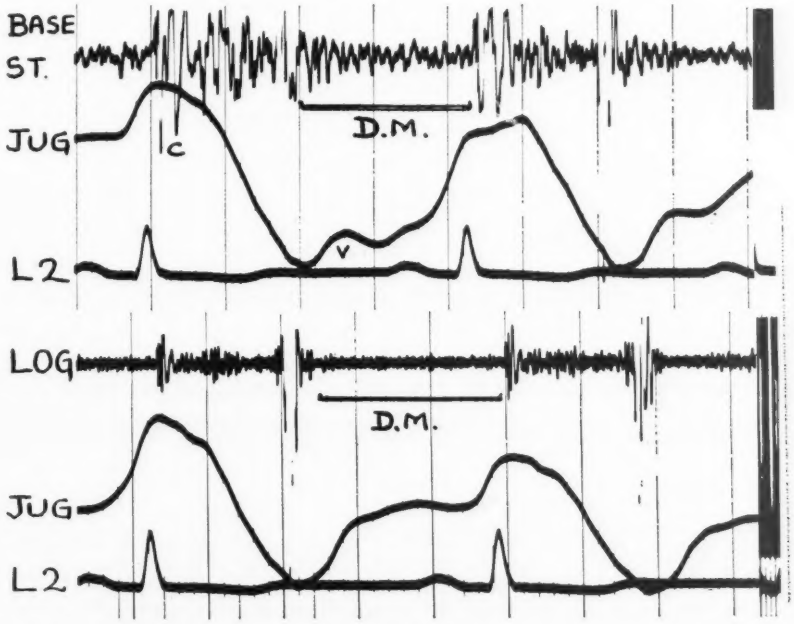

FIG. 9. Inaudible basal diastolic murmur. Basal diastolic murmur was not detected on auscultation because of fatiguing effect on the ear produced by the combination of the preceding systolic murmur and the markedly accentuated second sound. The stethoscopic record (upper) shows that the diastolic murmur (DM) actually is of high energy, but its intensity in the sensitive area of the frequency spectrum of hearing is low, as shown by the logarithmic record (lower). These audible vibrations are of much less amplitude in spite of the higher amplification used in the lower tracing as indicated by the wider standardization band on the right of the record.

and high pitched and accompanied the onset of the systolic murmur.[10] This was explained as due to the snapping upward of the fused pulmonic valve cusps at the onset of ventricular ejection. Recently[11] this has been shown phonocardiographically to be associated with an accentuation of the third component of the first heart sound, which is the element contributed by the opening of the semilunar valves. It has been called the "slatting sail" effect and is perhaps to be expected in valvular rather than infundibular stenosis. A similar phenomenon may occur in pulmonary hypertension alone, and also over the aortic area in aortic lesions,[12] and is explained as at times a vascular sound from the main pulmonic and aortic walls.

Leatham[13] stated that "the combination of a loud pulmonary systolic murmur with a second sound which is single, even during inspiration, is almost diagnostic of pulmonary stenosis or atresia, provided the patient is young and therefore splitting would normally be expected." We have shown with the phonocardiograph, however, that a pulmonic systolic murmur associated with delay in conduction

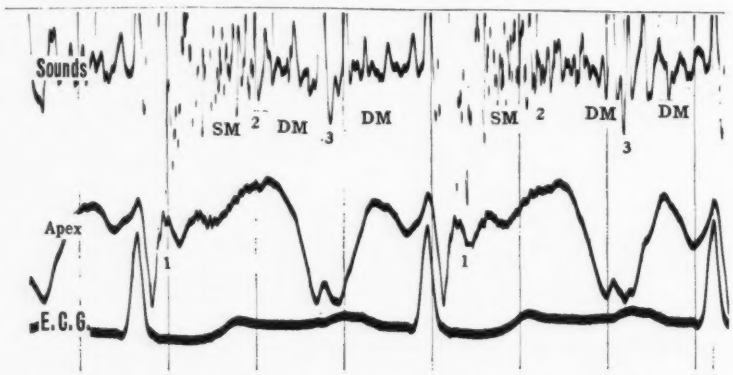

FIG. 10. Stethoscopic record from the apex of a 73 year old man with the clinical diagnosis of "rheumatic heart disease with mitral stenosis and regurgitation." There is a loud first heart sound preceded by a coarse low frequency vibration of auricular origin and followed by an intense systolic murmur which extends to the end of systole and obscures the second sound. A murmur fills diastole (DM) in which appears a loud third heart sound. Clinically the second sound was obscured by the systolic murmur and the third heart sound was mistaken for it. The intensity of the systolic murmur is shown by its detection in the apex cardiogram (linear).

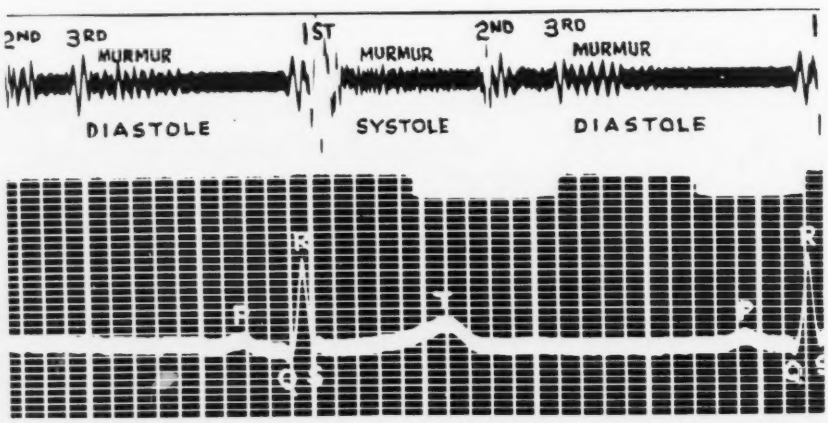

FIG. 11. Early mitral valve disease. The systolic murmur is present and the third sound followed by a short, mid-diastolic rumble with no presystolic phase.

the right ventricle in pulmonic stenosis will extend into left ventricular diastole and a cardiac catheter in the right ventricle in such a case will record an intraventricular pressure curve maintaining its systolic peak after collapse of the left ventricular carotid pulse wave (fig. 14).

Aortic regurgitation as a complication in patients with mitral stenosis in whom valvulotomy is being considered is at times difficult to differentiate from regurgitation through the pulmonary valve (Graham Steell murmur). Phonocardiography has not been definitive in this differential diagnosis. The pulmonary component of the second sound ordinarily follows the aortic, especially during inspiration, but an aortic diastolic murmur may be delayed in reaching maximal intensity so that it may appear to arise after the pulmonic valve sound. The musical murmur of an everted aortic cusp shows a characteristic pattern (fig. 15).

Aortic stenosis is now operable. In most instances the diagnosis may be made on auscultation with the combination of the loud systolic murmur (at times with thrill) and absent, or much diminished, second sound at the aortic area. Sometimes, however, mitral regurgita-

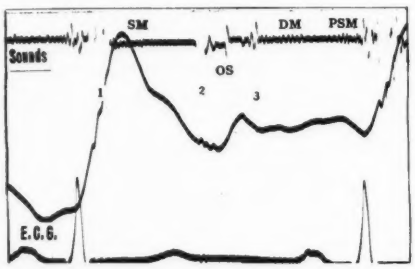

FIG. 12. Record from the apex of a 35 year old man with mitral stenosis two years after mitral valvuloplasty. No diastolic murmur was audible in the several months prior to operation, and he was severely incapacitated. The tracing shows the first, second, and third heart sounds. The opening snap (OS) appears in relation to the ascending limb of the "v" wave of the phlebogram (middle curve). The third sound is followed by a mid-diastolic murmur (DM) which disappears before the final presystolic phase (PSM) occurring with auricular systole.

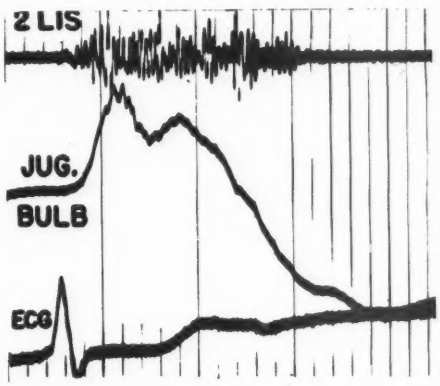

FIG. 13. The systolic murmur apparent in the upper tracing is shown to be tricuspid in origin since it appears so clearly in the venous tracing from the jugular bulb.

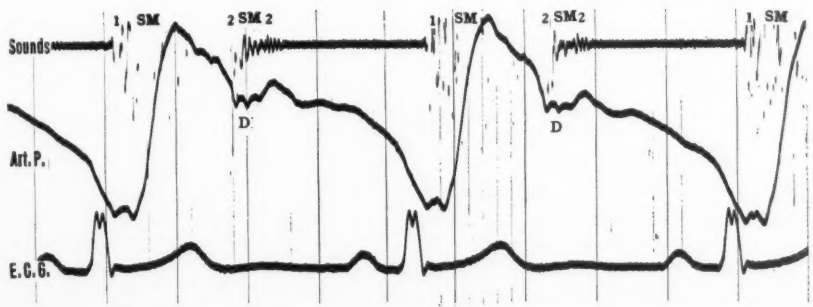

FIG. 14. Tracing taken over the pulmonic area in a patient with pulmonic valve stenosis and right bundle branch block. The middle curve is the arterial pressure. The systolic murmur can be seen to extend beyond the first element of the second sound. This element coincides with aortic valve closure as shown by its relation to the dicrotic notch (D) of the arterial pulse. The second component of the second sound is due to delayed pulmonary valve closure related to slow ejection from the right ventricle. In this patient these phenomena were further correlated with catheter pressure readings from the right ventricle which confirmed this interpretation.

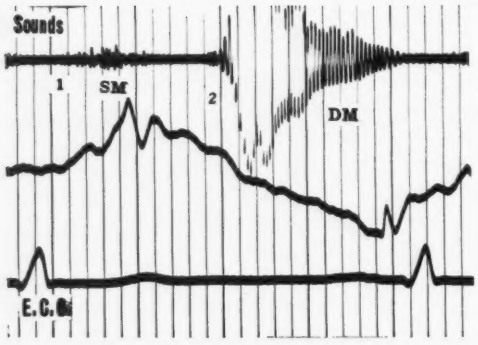

FIG. 15. Phonocardiogram taken at the aortic area of a 47 year old man with congestive failure secondary to an everted aortic cusp. Blood pressure 176/90–28. A low pitched, rough systolic murmur was heard in the aortic area and a grade 4 musical diastolic murmur in that area and in the third left intercostal space. The first sound is seen in the tracing to be very much diminished in this area; the systolic murmur (SM) is of low intensity. The second heart sound is somewhat delayed in its relationship to the end of the T wave of the electrocardiogram, and is followed by a loud crescendo-decrescendo diastolic murmur with a frequency averaging 112.5 cycles per second over a period of 0.4 second.

tion may resemble aortic stenosis since the systolic murmur of the latter condition may be well heard at the apex. Phonocardiography shows the murmur of aortic stenosis to be "diamond" shaped, starting somewhat after the first sound, reaching its maximum in mid systole and ending before the second sound. In mitral regurgitation the systolic murmur starts early and extends throughout systole up to the second sound. However, these typical patterns are not always to be relied upon in differential diagnosis.

CONCLUSIONS

Phonocardiography is a method of accessory value in a few cardiac conditions. It is technically a difficult procedure. It has been of greatest help in the timing of heart sounds having abnormal components or unusual accentuation of normal components—split sounds, third sounds, auricular sounds, and gallop rhythms.

In only rare instances are the data provided by phonocardiography of critical importance in diagnosis. Such instances include the recording of murmurs which are inaudible due to masking and fatigue effects on the ear from previous loud sounds; the demonstration of true presystolic murmurs of mitral stenosis; and the definition of characteristic patterns of pulmonic and aortic stenosis.

The discriminating use of phonocardiography will undoubtedly be increasingly helpful in the diagnosis of valvular and congenital heart disease.

REFERENCES

1 SPRAGUE, H. B.: A new combined stethoscope chest piece. J. A. M. A. **86:** 1909, 1926.

2 RAPPAPORT, M. B., AND SPRAGUE, H. B.: (a) Physiologic and physical laws that govern auscultation and their clinical application. Am. Heart J. **21:** 257, 1941; (b) The graphic registration of the normal heart sounds. Am. Heart J. **23:** 591, 1942.

3 COUNIHAN, T., MESSER, A. L., RAPPAPORT, M. B., AND SPRAGUE, H. B.: The initial vibrations of the first heart sound. Circulation **3:** 730, 1951.

4 ORÍAS, O., AND BRAUN-MENÉNDEZ, E.: The Heart Sounds in Normal and Pathological Conditions. New York, Oxford University Press, 1939.

5 ALIMURING, M., RAPPAPORT, M. B., AND SPRAGUE, H. B.: Phonocardiography and its clinical applications. Santo Tomas J. Med. (Manila) **4:** 115, 1949.

6 —, RAPPAPORT, M. B., AND SPRAGUE, H. B.: Variations in the first apical sound simulating the so-called "presystolic murmur of mitral stenosis." New England J. Med. **241:** 631, 1949.

7 WEISS, O., AND JOACHIM, G.: Registrierung von Herztönen und Herzgeräuschen mittels des Phonoskops und ihre Beziehungen zum Elektrokardiogramm. Ztschr. klin. Med. **73:** 240, 1911

8 COSSIO, P., AND BERCONSKY, I.: El Primer ruido cardiaco y el soplo presistólico en la estrechez mitral con fibrilación auricular. Rev. argent. cardiol. **10:** 162, 1943.

9 CURRENS, J. H., THOMPSON, W. B., RAPPAPORT, M. B., AND SPRAGUE, H. B.: Observations on the Flint murmur. New England J. Med. **248:** 583, 1953.

10 PETIT, A.: Rétrécissement pulmonaire. In Traité de Médecine de Charcot. Paris, Bouchard et Brissaud, 1902.

11 NADAS, A., AND DOW, J. W.: Personal communication.

12 CALO, A.: Les Bruits du Coeur et des Vaisseaux. Paris, Masson et Cie, 1950. P. 302.

13 LEATHAM, A.: Phonocardiography. Brit. M. Bull. **8:** 333, 1952.

ABSTRACTS

CORONARY ARTERY DISEASE

Slapak, L.: On Auricular Involvement in Myocardial Infarction. Cardiologia **22**: 228 (Fasc. 4), 1953.

Ten personal observations of recent and old myocardial infarction involving the auricles (3.12 per cent of the entire examined autopsy material) are reported and the literature on the subject is reviewed. In seven cases this was associated with posterior wall infarction, in one with anterior wall infarction, and in two with infarction of both ventricular walls. In all instances the right auricle was involved (eight times its anterior and two times its posterior wall), and in five instances the left auricle also (three times the posterior and two times the anterior wall).

The electrocardiographic alterations which can be attributed to auricular infarction are discussed. In the present series electrocardiograms were available in eight instances. In six cases there was a disturbance of rhythm (A-V block, auricular flutter and fibrillation, and premature beats), and in two cases a displacement of the P-Q segment. In two cases with conduction disturbance the diagnosis was suspected during life. The author thinks, that auricular infarction is more common than would appear from the scanty reports in the literature. One of the reasons for the paucity of reported cases is probably the fact that insufficient attention is paid by the pathologist to infarcted areas in the auricles.

PICK

Russek, H. I., Russek, A. S., Doerner, A. A., and Tohman, B. L.: Cortisone in Treatment of Shoulder-Hand Syndrome Following Acute Myocardial Infarction. Arch. Int. Med. **91**: 487 (April), 1953.

Cortisone was employed in the treatment of 17 patients with shoulder-hand syndrome which developed as a complication of acute myocardial infarction. In all these patients previous treatment with physical therapy, manipulative therapy, or local and stellate ganglion blocks was without significant effect. Cortisone produced complete relief of signs and symptoms in five patients, marked improvement in eight, moderate improvement in three, and no significant response in one. The striking feature of the treatment was its dramatic effect in the relief of pain, often within 24 to 48 hours. In addition, there was concomitant but often less marked improvement in the range of motion at affected joints. Vasomotor disturbances were also rapidly influenced with decrease or disappearance of edema and improvement in temperature, color, and sudomotor activity of the hand. In patients responding favorably there was no recurrence of symptoms after discontinuance of treatment. No thromboembolic complications were encountered in this series. These and previous observations fail to confirm the serious risk of vascular complications which is claimed to result from the use of this drug.

BERNSTEIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, AND BALLISTOCARDIOGRAPHY

Froment, R., Gallavardin, L., and Cahen, P.: Paroxysmal Ventricular Tachycardia: A Clinical Classification. Brit. Heart J. **15**: 172 (April), 1953.

The authors classify paroxysmal ventricular tachycardia as follows. (1) A terminal prefibrillatory type that indicates the preterminal decline of an exhausted myocardium; it is characterized by electrical polymorphism and frequently associated with digitalis medication. (2) A type associated with

curable and mild monomorphic ventricular premature beats; this type usually affects young adults and is refractory to treatment. There are almost permanent monomorphic premature beats irregularly interspersed with paroxysms of tachycardia; these are of brief duration except in severe forms when they may be prolonged and interrupted at long intervals by sinus beats. This is a rare benign functional disorder that may produce vertigo, faintness or, rarely, transient heart failure. (3) A type due to infarction or, rarely, syphilis of the ventricular septum. (4) A persistent and prolonged type that occurs in sound hearts usually in young people: this type differs from type 2 in the absence of isolated ventricular premature beats and is similar to supraventricular tachycardia in its abrupt onset and offset, however, the duration of the attack is longer, lasting for several days to a week. The rate is high (159 to 243). Postparoxysmal electrical changes may persist for as long as two months but have no prognostic significance.

SOLOFF

Sanabria, T.: Anatomic-Pathologic Study in Bundle Branch Block. Acta cardiol. **8:** 145 (Fasc. 2), 1953.

The author studied in serial sections the histology of the A-V conduction system in two cases with a typical pattern of left bundle branch block, in one case with right bundle branch block, and in one case with intermittent (left) bundle branch block. In none of them was an anatomic lesion of the bundle branches or the common bundle found. Conversely, of two other cases who had definite destructive lesions in one or in both bundle branches, one had a nonspecific abnormal electrocardiographic pattern and the other, complete A-V dissociation; the QRS duration was normal in both.

These findings suggest that the electrocardiographic pattern of bundle branch block is not necessarily due to a localized anatomic interruption of the conduction pathways in the ventricles. It may apparently be caused by more widespread alterations which cannot be demonstrated morphologically. Therefore, according to the author, the classic concepts of bundle branch block need some revision.

PICK

Glatt, R.: The Electrocardiogram of Flying Pilots Transmitted by Radio. Cardiologia **22:** 238 (Fasc. 4), 1953.

A method is described for wireless recording of electrocardiograms of pilots during flight. The transmission is achieved by means of a frequency modulating device connected to the standard aircraft radio transmitter. With this arrangement electrocardiograms can be recorded on the ground in one or in several leads without artefacts or atmospheric distortions. Several such tracings of pilots flying a "De Havilland Vampire" are reproduced. The described method is appropriate for cardiologic-physiologic control of persons flying in high altitudes.

PICK

Szekely, P., and Snaith, L.: Paroxysmal Tachycardia in Pregnancy. Brit. Heart J. **15:** 195 (April), 1953.

Ten instances of paroxysmal tachycardia were observed over a 10-year period among 10,746 pregnant patients of whom 380 had heart disease. The tachycardias were of the supraventricular type. In the absence of structural heart disease, the arrythmia does not interfere with the course of normal pregnancy. Pregnancy appears to increase susceptibility to this arrhythmia.

SOLOFF

Shearn, M. A., and Rytand, D. A.: Intermittent Bundle-Branch Block. Arch. Int. Med. **91:** 448 (April), 1953.

Several unusual electrocardiograms are reported. In one, gradual transition from normal to bundle-branch block complexes occurs over a six-cycle interval; in another, from a patient with auricular tachycardia, the pattern of acute myocardial infarction concealed by left bundle-branch block becomes unmasked coincident with the development of a 2 to 1 auriculoventricular block. The importance of the critical heart rate with respect to intraventricular conduction is emphasized, and its significance is discussed. It is suggested that the determination of the critical rate is a convenient method of following the progress of a case of intermittent bundle-branch block. From this and other studies, it appears that intermittent bundle-branch block is usually an expression of underlying myocardial disease and probably represents a transitional stage before permanent bundle-branch block supervenes.

BERNSTEIN

Modugnos, G., and Besasso, E.: Electrocardiographic Modifications in the Course of Cholecystopathies. Acta cardiol. **8:** 135 (Fasc. 2), 1953.

In 32 cases with gall bladder disease a frequent finding was lowering of the T waves (in 48 per cent) and inversion of the T waves in lead III (in 49.5 per cent). These alterations disappeared with contraction of the gall bladder, following duodenal lavage, or after intravenous injection of ergotamine. The authors believe that these electrocardiographic alterations are caused by sympathetic stimulation subsequent to distension of the gall bladder, and may be of value in the diagnosis of gall bladder disease.

PICK

Scarborough, W. R., Davis, F. W. Jr., Baker, B. M. Jr., Mason, R. E., Singewald, M. L.,

Lore, S. A., and Fox, L. M.: The Ballistocardiographic Study of 369 Apparently Normal Persons. An Analysis of "Normal" and "Borderline" Ballistocardiograms. Am. Heart J. **45:** 161 (Feb.), 1953.

Ballistocardiographic records taken on a Starr-type high frequency bed together with electrocardiographic studies were made on 369 clinically normal persons—261 men and 108 women, ranging in age from 20 to 84 years. There were no abnormal ballistocardiograms in individuals under the age of 40, but from the fifth decade to the eighth, the incidence of abnormal ballistocardiograms rose step-wise from 10 per cent to 91.7 per cent. For the same decades, the incidence of abnormal electrocardiograms rose from 2.6 per cent to only 8.3 per cent. In the entire group of 369 individuals the ballistocardiograms were normal in 55.8 per cent, borderline in 9 per cent, and abnormal in 25.2 per cent; the corresponding figures for the electrocardiograms were 90.5 per cent, 6.8 per cent and 2.7 per cent.

A detailed quantitative analysis was made of approximately sixty variables from 275 normal and borderline ballistocardiograms. These include time interval measurements of the waves, and their relationship to age, sex, pulse rate and body size. A further study was made of some of the factors influencing the amplitude and duration of the ballistic complex, respiratory variation, cardiac output, ballistic "vector" distribution, and other ballistocardiographic variables.

Based on this data, preliminary, empiric criteria for the normal ballistocardiogram were determined. The authors state that at present the attitude towards the ballistocardiogram should be as follows: if the ballistocardiographic interpretation coincides with the other clinical and laboratory data, it may be given weight, but, if on the other hand, the ballistocardiogram is abnormal in the absence of any other confirmatory findings, then one should reserve opinion on its clinical significance.

RINZLER

Ivancic, R., and Mikulnic, V.: Determination and Calculation of the Spatial Ventricular Gradient with the Aid of Bipolar Transthoracic Leads. Acta cardiol. **8:** 163 (Fasc. 2), 1953.

The usual determination of the ventricular gradient is made in the frontal plane. The authors describe a method for determination of its spatial position using a certain arrangement of electrodes corresponding to three perpendicular transthoracic leads. With this method it can be shown that under normal conditions, the vector representing the ventricular gradient is directed downwards, to the left, and posteriorly. Thus, it is located in the left posterior lower quadrant of a three dimensional system of coordinates.

PICK

Wenger, R., Doneff, D., and Moser, K.: The Diagnostic Significance of the Vectorcardiogram in the Recognition of Incomplete Right and Left Bundle Branch Block Types. Ztschr. Kreislaufforsch. **42:** 161 (March), 1953.

The authors report vectorcardiographic studies of cases who in the conventional electrocardiogram showed patterns of incomplete intraventricular blocks. A right sided conduction defect of this type is suggested by a slurred S wave in leads I and II and a notching of QRS in the right precordial leads, in the absence of abnormal QRS prolongation. Such patterns occur in normals, for example in asthenic types, as well as under pathologic conditions, for example in right ventricular hypertrophy. A vectorcardiogram in the horizontal plane permits, according to the authors, a distinction between the two possibilities. In normal persons it will show a single smooth QRS loop; in the presence of an abnormal conduction delay, a double QRS loop, with the first portion pointing to the left and the second, terminal one, pointing to the right and anteriorly.

The diagnosis of a left sided complete or incomplete intraventricular block is suggested by reversal of the direction of the development of the QRS loop in the horizontal vectorcardiogram, so that it takes place in a clockwise direction instead of the normal conterclockwise manner, as is seen in left ventricular hypertrophy without abnormal delay of left ventricular activation.

PICK

Doyle, A. E.: Electrocardiographic Changes in Hypertension Treated by Methonium Compounds. Am. Heart J. **45:** 363 (March), 1953.

Serial electrocardiograms were taken before and after treatment with the methonium compounds in 75 patients with arterial hypertension. Sixty had essential and 15 malignant hypertension. The majority of the patients were treated with subcutaneous injections of hexamethonium bromide; a few received oral hexamethonium bitartrate and a few, subcutaneous injections of M. & B. 1863. These patients were treated for at least three months. In no patient was digitalis administered.

Electrocardiograms from 54 patients with S-T or T-wave abnormalities showed a return to normal in 26 patients and a return toward normality in 20. Electrocardiograms from 50 patients with abnormally high QRS voltage showed a return to normal in 32 and a return in the direction of normal in six. Such improvements in the electrocardiogram appeared to be directly related to the degree of control of blood pressure achieved.

RINZLER

Schaffer, A. I., Bergmann, P. G., Boyd, L. J., Mirkinson, A., and Beinfield, W. H.: Eccentricity as a Cause for the Difference Between the Vectorcardiograms Registered by the Cube and

Tetrahedral Systems. Am. Heart J. **45:** 448 (March), 1953.

This report attempts to show how the eccentric position of the heart in the trunk is the cause for much of the observed difference between the vectorcardiograms registered by the cube system and those registered by the tetrahedral system. The authors make a distinction between the anatomic and effective axis of the lead and have set up a diagram and table which correlate the deviations of the effective axis of homologous leads with the differences in the manifestations of the two systems. To test the validity of the diagram and table, a group of newborn infants were examined by the cube and tetrahedral systems and the manifest vectors showed certain differences which agreed very well with the expected differences as set forth in the diagram and table. The authors conclude that eccentricity is significant not only in the newborn but also in the adult and suggest that these methods for treating the eccentricity factor could be applied (a) in choosing a lead system for vectorcardiography, (b) in interpreting the shift of the manifest vector due to changes in body position, and (c) in explaining the posterior orientation of the cube loops in marked right ventricular preponderance.

RINZLER

Kissin, M., and Schwarzschild, M. M.: The Measurements of Time Intervals in the Electrocardiogram. Cardiologia **22:** 218 (Fasc. 4), 1953.

In order to define criteria for precise measurements of the width of electrocardiographic deflections and intervals, the authors studied the effects of alteration of the amplitude of a deflection upon its apparent duration in artificial electrocardiograms. They arrived at the following conclusions:

A wave of high amplitude appears to have a longer duration than an identical wave of low amplitude. The beginning and the end of a wave may appear isoelectric in one of the limb leads, or, rarely in all three of them, but it cannot be of zero potential in two limb leads only. Therefore the longest P, QRS, QT or T in any lead is the correct one. If the P-R interval varies in duration, neither the longest nor the shortest is the correct one, but rather a P-R of intermediate duration. The correct P-R will also be found in the greatest number of leads. To determine which one of the three limb leads shows the correct beginning and end of a particular wave, and to include in the measurement misleading isoelectric portions in some of the leads, the following rules were developed: if the initial (or terminal) part of a deflection has the same direction in I and III, then lead II is correct; if the direction is opposite in I and III, the lead is correct which is in the same direction as lead II. For "unipolar" limb leads that lead is correct in which the deflection is opposite to the other two.

PICK

Buckingham, W. B., Sutton, G. C., Wendel, G., and Sutton, D. C.: A Pharmacodynamic Study of the Relationship Between Hypertension and the Deep K Stroke Pattern of the Ballistocardiogram. Quart. Bull. Northwestern Univ. M. School **27:** 21 (Spring), 1953.

The deep K stroke type of the abnormal ballistocardiogram has been observed in normal individuals under the pharmacologic conditions that increase cardiac work. When patients with hypertensive heart disease and deep K stroke ballistocardiograms are temporarily made normotensive without significant change in the cardiac-work, the deep K stroke pattern persists. This is interpreted to mean that the deep K stroke pattern may be an expression of increased cardiac work, and not a specific pattern of a specific disease.

BERNSTEIN

Reynolds, G.: The Atrial Electrogram in Mitral Stenosis. Brit. Heart J. **15:** 250 (April), 1953.

During operation of mitral commissurotomy, electrograms were taken from the outer surfaces of the right and left atria in 29 instances. For comparison, similar investigations were made in 11 with congenital heart disease and in 8 with carcinoma of the esophagus.

Compared with the controls, the voltage was increased in the left atrial tracings in mitral stenosis and in the right atrial tracings in congenital heart disease. Asynchronism of the P waves was present in all tracings, and greatest in those with mitral stenosis. The first peak is derived from the right atrium.

SOLOFF

Welsch, A., and Wieland, N.: Concerning the Clinical Value of the Ventricular Gradient. Studies in Electrocardiograms with Right Preponderance. Ztschr. Kreislaufforsch. **42:** 262 (April), 1953.

In order to test the clinical importance of determinations of the ventricular gradient, the authors defined the QRS and T areas in 120 electrocardiograms, showing in the standard leads some degree of right axis deviation, and then constructed the ventricular gradient. In 15 cases the results were correlated with autopsy findings.

In healthy individuals AQRS ranged between 13 and 69 mv seconds, and G between 34 and 120 mv seconds. G was invariably located to the left of AQRS, maximal at an angle of 30 degrees. Similar data were obtained in pulmonary emphysema without evidence of right heart pathology. In mitral lesions with right heart failure the gradient was usually small and deviated to the left. In chronic cor pulmonale and in kyphoscoliotic heart disease, abnormalities of the ventricular gradient were in no relation to the degree of right heart involvement found at necropsy, but a good correlation was found

in three cases of congenital heart disease. In myocardial infarction the direction of the abnormal vector component compared well with the site of infarction found at autopsy, except in cases who had more than a single infarct.

The ventricular gradient represents the frontal projection of electromotive forces resulting from inhomogenous regression of ventricular activation and is, under normal conditions, dependent upon forces developed in the left ventricle. If more than a single lesion is present, for instance, bilateral ventricular hypertrophy or severe damage to the myocardium of both ventricles, the conditions determining the direction and magnitude of this vector become very complex. In such cases the empiric morphologic evaluation of a multiple lead electrocardiogram is superior to the determination of the ventricular gradient.

PICK

ENDOCRINE EFFECTS ON CIRCULATION

Sensenbach, W., Madison, L., and Ochs, L.: The Effect of ACTH and Cortisone on Cerebral Blood Flow and Metabolism. J. Clin. Investigation **32:** 372 (April), 1953.

Patients undergoing therapy with corticotropin (ACTH) and cortisone may have changes in personality, mood, or may develop frankly psychotic episodes. To investigate the cerebral, hemodynamic, and metabolic effects of these hormones, the authors studied 12 patients receiving corticotropin and nine patients receiving cortisone, and, in addition, two patients with Cushing's syndrome. Observations were made before, during, and after treatment. In both the cortisone- and corticotropin-treated patients there were parallel increases in the mean arterial blood pressure and cerebral vascular resistance, although the mean cerebral blood flow remained unchanged. These results suggest that the cerebral circulation shares in the increased general peripheral vascular resistance, but that there was no specific or localized effect on the cerebral blood vessels. Similar changes were found in two subjects with Cushing's syndrome. These studies then do not explain the mental changes that occurred during administration of the hormones.

WAIFE

HYPERTENSION

Katz, L. B., Rhodes, G. J., George, R. S., and Moses, C.: Total Serum Cholesterol, Cholesterol-Lipid Phosphorus Ratio and S_f 12–20 Concentration in Hypertension, Diabetes, and Coronary Artery Disease. Am. J. M. Sc. **225:** 120 (Feb.), 1953.

A large number of patients, including those with hypertension, diabetes, and coronary artery disease, as well as control subjects were studied with respect to total serum cholesterol, S_f 12–20 lipoprotein concentration and cholesterol-lipid phosphorus ratio. The results were tabulated separately for sexes and for each individual group. There were no significant differences in the mean total cholesterol values among any of these groups. The S_f 12–20 data did not reveal significant differences among the male groups, but the mean values for the female patient groups were significantly higher than for the female controls. However, the wide range of values obtained limits the clinical usefulness of this procedure. The cholesterol-lipid phosphorus ratios were lower in diabetic males than in other groups, but again, there was considerable overlapping of values. The authors conclude that the wide range of values obtained by each of these methods in normal subjects and in patients with hypertension, diabetes, and coronary artery disease indicates that the findings in individual cases must be interpreted cautiously until more information concerning their significance in the pathogenesis of vascular disease is available.

SHUMAN

Magill, I. W., Scurr, F. C., and Wyman, J. B.: Controlled Hypertension by a Thiophanium Derivative. Lancet **1:** 219 (Jan. 31), 1953.

From a study of five patients in whom a thiophanium derivative (a ganglionic blocking agent) was administered to anesthetized patients by intravenous drip, the authors observed (1) that the degree of hypotension was directly related to the amount of the agent given, without development of increasing resistance, and (2) that recovery was rapid after the agent was discontinued.

MCKUSICK

Khan, M. A.: Effect of Hydralazine in Hypertension. Brit. M. J. **1:** 27 (Jan. 3), 1953.

The author could demonstrate no significant long-term reduction in blood pressure in 12 hypertensive patients to whom 1-Hydrazinophthalazine in daily dosage up to 1200 mg. was administered. He could demonstrate no potentiation of the effect of hexamethonium. Unpleasant side-effects were almost universal and persistent.

MCKUSICK

Wilkins, R. W., and Judson, W. E.: The Use of Rauwolfia Serpentina in Hypertensive Patients. New England J. Med. **248:** 48 (Jan.), 1953.

The results of observations of the effect of Rauwolfia serpentina (ophioxylon serpentinum) in over 100 patients studied for periods of one month to one year are reported in this communication. The oral dose of one to three tablets daily was well tolerated with no serious side effects. The action was slow to appear and disappear. The drug promoted a moderate hypotension, particularly in labile patients with hypertension and tachycardia. It caused sedation, bradycardia, nasal congestion, some gain in

weight, and tended to change the bowel habit to slightly increased frequency. It did not seem to cause tolerance nor did it appear habit forming. It seemed most useful as an adjunct to more powerful hypotensive drugs such as Veratrum viride or hydrazinophthalazine. Serpina alone appeared to be of modest potency as a hypotensive agent and reduced the pressure to normal only when it was moderately elevated. In 18 patients who failed to respond to a combination of Serpina and Veratrum viride or hydrazinophthalazine, all three drugs were used together, often with a further reduction in the blood pressure. The bradycardia produced by the drug is not abolished by intravenous injection of atropine, an observation which suggests that this effect is not due to vagal hyperactivity. Symptomatic improvement was often quite striking in patients receiving this drug.

ROSENBAUM

Glushien, A. S., Mansuy, M. M., and Littman, D. S.: Pheochromocytoma. Its Relationship to the Neurocutaneous Syndromes. Am. J. Med. **14:** 318 (March), 1953.

Reporting three cases of pheochromocytoma, one associated with multiple neurofibromatosis and two with von Hippel-Lindau disease, the authors postulate that a pheochromocytoma is related not only to multiple neurofibromatosis, but also to von Hippel-Lindau disease and perhaps to other neurocutaneous syndromes such as tuberous sclerosis and Sturge-Weber syndrome (encephalotrigeminal angiomatosis). Eighteen cases of multiple neurofibromatosis associated with pheochromocytoma have been found in the literature. The authors suggest that in operations for pheochromocytoma upon patients with neurofibromatosis or von Hippel-Lindau disease the left adrenal region should be explored first. The incidence of neurocutaneous syndromes among patients with pheochromocytoma is estimated to be at least 10 per cent. Stigmas of neurocutaneous disease or any developmental anomaly in a hypertensive patient should arouse suspicion of pheochromocytoma. The long-term prognosis for patients from whom a pheochromocytoma has been removed may not be as good as is generally believed.

HARRIS

Schottstaedt, M. F., and Sokolow, M.: The Natural History and Course of Hypertension with Papilledema (Malignant Hypertension). Am. Heart J. **45:** 331 (Mar.), 1953.

The general features of the 104 patients with malignant hypertension in this study were as follows: (1) the average age was 42 years; (2) the ratio of men to women was 3 to 2; (3) a family history was found in half the patients; (4) knowledge of preexisting hypertension was present in 71 per cent of the group; and (5) significant past illnesses (scarlet fever or frequent sore throats, glomerulonephritis, pyelonephritis, and toxemia of pregnancy) had occurred in 56 per cent of the patients. Impairment of vision was considered to have marked the onset of the malignant state in 78 cases, gross hematuria in five and severe headaches alone in six. The average estimated duration of the malignant phase was 8.7 months, with a range of two weeks to six and one-half years. The average survival after the discovery of papilledema was 8.4 months, with a range of one day to seven years. In three instances, a spontaneous remission occurred. The more sudden and severe the onset with headaches, congestive failure, gastrointestinal complaints, and the "fatigue complex," the more likely was a rapid progression into the malignant phase.

The effects of malignant hypertension on various organ systems were analyzed. Ninety per cent had impairment of vision during their illness, with papilledema, vascular changes, and exudates present in all at some time during the course, and hemorrhages in all but eight patients. Three-fourths of the patients had symptoms of cardiac failure, while half had signs confirming its presence. Seventy-five per cent had enlarged hearts on x-ray examination; 90 per cent of the electrocardiograms were abnormal. The blood pressure levels ranged from 300–160/180–100 mm. Hg to 265–90/150–60 mm. Hg. Cerebrovascular disturbances were manifested in 44 patients and consisted of "strokes" and convulsions. Eighty-four per cent had symptoms relating to the kidney and all patients had some abnormality demonstrable by one or more laboratory tests. The basic renal lesions found at post mortem were nephrosclerosis in 14 cases, glomerulonephritis in 7, and pyelonephritis in 12. A bleeding tendency occurred in 57 per cent of the patients; uremia was twice as common in this group as in the remaining patients. A moderate or severe anemia was present in half of the group when papilledema was discovered.

RINZLER

Smirk, F. H.: Action of a New Methonium Compound in Arterial Hypertension. Pentamethylene 1:5-bis-N (N-methyl-pyrrolidinium) Bitartrate (M. and B. 2050A). Lancet **1:** 457 (March 7), 1953.

This agent proved five times more effective than hexamethonium and had a more prolonged action. There were fewer side effects than with previous agents in this group. Only partial cross-tolerance developed between it and hexamethonium. As with hexamethonium, perfectly quiet standing for 60 seconds or until faintness developed proved one of the best methods by which the patient could regulate his own dosage. As with C_6 further drop in blood pressure occurred if a meal was eaten after a dose of the agent, due presumably to inability of

r flex compensation for splanchnic vasodilatation. E xperience with both oral and subcutaneous administration is described.

McKusick

Collman, A., and Shapiro, A. P.: The Volume of the Extracellular Fluid in Experimental and Human Hypertension. J. Clin. Investigation **32**: 312 (April), 1953.

A group of dogs were rendered hypertensive by application of a ligature to one kidney and removal of another. Both mannitol and radioactive sulfate were used to determine the extracellular volume. Similar studies were performed in 12 normotensive and 14 hypertensive patients.

The authors observed an increase in the extracellular volume in hypertension. There was no correlation between the extracellular fluid volume and the level of the blood pressure. The conclusions assume that the mannitol and radioactive spaces represent extracellular fluid volume both in the normal as well as in the hypertensive subject.

Waife

Esselier, A. F., Luscher, W., and Morandi, L.: Hydrazinophthalazine in Hypertension. A Clinical Study. Schweiz. med. Wchnschr. **83**: 340 (April), 1953.

1-Hydrazinophthalazine (Apresoline) and 1,4-dihydrazinophthalazine (Nepresol) were tested in a number of cases with essential and renal hypertension. Both drugs have a pressure reducing effect. With continuous medication the blood pressure can be lowered, but not normalized in about 50 per cent of the cases. Better response was observed in essential hypertension than in the nephrogenic type. Side effects are common and unpleasant, always reversible, but may interfere with continuation of therapy. Nepresol appears somewhat superior to Apresoline as regards tolerance and activity, but both agents require more clinical testing.

Pick

Merz, W. R.: Fatal Pulmonary Embolism in the Course of Anticoagulant Treatment. Schweiz. med. Wchnschr. **83**: 407 (April), 1953.

The author collected from various hospitals in Switzerland 10 case histories of thrombophlebitis in whom fatal pulmonary emboli occurred during treatment with anticoagulants. In retrospect, in all instances the cause could be traced to either inadequate dosage or to early interruption of the therapy. The former occurs especially during the transition from Heparin to other anticoagulants. The author recommends the maintenance of patients with thrombophlebitis on Heparin treatment, and the use of at least 40 000 IE-24 daily for at least three weeks.

Pick

Moyer, J. H.: Hydrallazine Hydrochloride. Arch. Int. Med. **91**: 419 (April), 1953.

The acute (three months) and long term (one to two years) therapeutic results in 54 hypertensive patients treated with hydrallazine (1-hydrazinophthalazine, Apresoline) as the only form of hypotensive therapy are presented. Evaluation after three months of therapy indicates that 35 per cent of the patients obtained a significant reduction (more than 20 mm. mean blood pressure) in blood pressure. After one to two years of therapy only 9 per cent of the patients continued to obtain adequate blood pressure regulation. Treatment with hexamethonium alone resulted in therapeutic failure in 20 patients, and treatment with hydrallazine alone failed in 32. These patients were then given combined hexamethonium and hydrallazine therapy. With this regimen 75 per cent of the patients for whom therapy had previously failed obtained a significant reduction in blood pressure or the blood pressure was better stabilized.

Some of the pharmacodynamics of hydrallazine are presented. The drug apparently reduces the blood pressure through a central vasodepressor action. At the same time it stimulates (centrally) the sympathetic nerves to the heart, causing tachycardia and increased cardiac output. During continued oral therapy the cardiac stimulant effect is blocked off if hexamethonium has previously been given in amounts adequate to produce ganglionic blockade (partial). Hydrallazine reinforces the hypotensive effect of hexamethonium when the former drug is given after the latter. This form of combined therapy may produce a dramatic and sudden reduction in blood pressure, which in the presence of severe renal damage may be associated with a significant reduction in glomerular filtration rate and renal excretory function. Therefore, careful evaluation of changes in renal excretory function by repeated blood urea nitrogen determinations is necessary when treating hypertensive patients with associated renal damage of an advanced degree.

Bernstein

PATHOLOGIC PHYSIOLOGY

Boniface, K. J., and Brown, J. M.: Effect of Carbon Dioxide Excess on Contractile Force of Heart, in Situ. Am. J. Physiol. **172**: 752 (March), 1953.

The effect of carbon dioxide mixtures on the contractile force of right ventricular segments was measured. Both the heart contractile force and the amplitude of systolic excursion decreased and were associated with pronounced dilation. The concentration of carbon dioxide in the respired gas mixture was approximately proportional to the amount and speed of the changes produced. The heart sometimes recovered its force although exposure to carbon dioxide continued. This is different from the

effect of the other common cardiac depressants. On some occasions when the administration of carbon dioxide was terminated a "rebound" effect was seen.

OPPENHEIMER

Selfurt, E. E.: Influence of Hypoxia on Renal Circulation and on Excretion of Electrolytes and Water. Am. J. Physiol. **172:** 700 (March), 1953.

In these experiments one kidney was perfused with venous blood from the right ventricle. Hypoxia of the kidney was obtained while the rest of the animal was disturbed hardly at all. Oxygen of venous perfusion blood had an average of 10.7 volumes per cent. Para-aminohippurate clearance increased 22 per cent indicating a hyperemia. Renal vascular resistance was decreased. The filtration fraction was lessened. There was usually an increase in the excretion of sodium, potassium, and water. The author has concluded that these last results are due to a small reduction in the tubular reabsorption of these substances.

OPPENHEIMER

Lenègre, J., Scebat, L., Besson, H., Benchemoul, F., and Damien, J.: The Pulmonary Capillary Pressure in Various Types of Heart Disease. Arch. mal. coeur **46:** 1 (Jan.), 1953.

The authors studied pulmonary capillary pressure curves in 134 cases which included normals, various types of heart disease, chronic pulmonary disease, and combinations of the latter.

In the normal, the pulmonary capillary pressure is 3 to 10 cm. H_2O and is closely related to the pressure in the pulmonary veins and in the left auricle. This value does not significantly change on exercise or emotion. The pulmonary capillary venous pressure is elevated in all conditions with some resistance to the emptying of the pulmonary veins. This refers to mitral stenosis as well as to left ventricular failure of aortic or arterial (hypertensive) origin, and to chronic constrictive pericarditis. In all these conditions additional pressure elevation occurs under stress. The highest values of pulmonary capillary pressure are reached during attacks of pulmonary edema where the tension exceeds 47 cm. H_2O and thus, by far, the oncotic pressure. Hence, acute pulmonary capillary hypertension is probably the dominant factor in the events leading to transudation of edema fluid into the pulmonary alveoli. The pulmonary capillary pressure is normal in congenital heart disease with chronic right heart strain, in chronic cor pulmonale, and in other conditions associated with pulmonary hypertension.

The authors conclude that determinations of the pulmonary capillary pressure are not of great practical importance but may contribute to differentiate between left heart failure and chronic constrictive pericarditis, or mitral disease and certain types of chronic pulmonary disease. Furthermore, they are necessary for the calculation of pulmonary vascular resistance.

PICK

Sokoloff, L., Wechsler, R. L., Mangold, R., Balls, K., and Kety, S. S.: Cerebral Blood Flow and Oxygen Consumption in Hyperthyroidism before and after Treatment. J. Clin. Investigation **32:** 202 (March), 1953.

The cerebral blood flow was determined in 11 patients with hyperthyroidism. It was found that the same oxygen consumption, both before and after effective therapy, as well as the lack of a significant difference between this oxygen consumption and that of a normal group of comparable age, suggests that cerebral metabolism is unaltered in hyperthyroidism. It would appear that the gross energy metabolism of the brain, as reflected by the oxygen utilization, may be independent of the action of the thyroid hormone.

WAIFE

Muenchinger, R.: Investigations Concerning the Activity of Adenosine triphosphatase in the Heart Muscle, a Contribution to the Pathogenesis of the So-Called Energetic Dynamic Cardiac Insufficiency. Cardiologia **22:** 145 (Fasc. 3), 1953.

In certain abnormalities of the electrolyte balance and in intoxication, a syndrome occurs which is described by Hegglin under the term "energetic dynamic cardiac insufficiency." The primary disturbance is a reduction in the force of contraction which results from the metabolic disorder recognized by the prolongation of the Q-T interval in the presence of a prematurity of the second heart sound. Under the assumption that this disorder might be related to some alteration of adenosine triphosphate (ATP), and/or an enzyme acting on it (adenosinetriphosphatase, ATPase), the effect of a number of electrolytes and drugs on the activity of ATPase was investigated, using a method described by Dubois and Potter.

Data are presented indicating that the action of adenosinetriphosphatase is enhanced by the chlorides of potassium, sodium, calcium and magnesium, and by cardiac glycosides like Strophosid and Digilanid; it is inhibited by veratrine, urethane, fluoride, oxalate, chloralhydrate, and copper sulfate. Acetylcholine, adrenaline, pilocarpine, desoxycorticosterone potassium cyanide, morphine hydrochloride, veronal sodium, sodium arsenate, sodium salicylate, and picrotoxine have but little effect on adenosinetriphosphatase activity.

The results of this investigation are discussed in terms of the relationship between the activity of adenosinetriphosphatase and the electrocardiographic manifestations of energetic dynamic cardiac insufficiency. Both prolongation and shortening of the Q-T interval seem to be caused by a disorder

n the function of this enzyme, the former by depression, and the latter, by enhancement of its activity n the myocardium.

PICK

Haddy, F. J., and Campbell, G. S.: Pulmonary Vascular Resistance in Anesthetized Dogs. Am. J. Physiol. **172:** 747 (March), 1953.

Pressures were measured in the pulmonary veins f dogs under pentobarbital anesthesia. Pressures ere increased by either inspiratory or expiratory irway resistance breathing or by increased intraranial pressure. In these experiments pulmonary ascular pressure gradients decreased. Nevertheless lood flow was essentially unchanged. Pulmonary ascular resistance decreased as pulmonary vein pressure was increased. It is pointed out that the absolute level of intraluminal pressure over external pressure plays a large role in determining the pulmonary vessel diameter. This in turn determines the resistance.

OPPENHEIMER

Hebert, J., Scebat, L., and Lenègre, J.: Incidents and Accidents in Right Heart Catheterization. Arch. mal. coeur **46:** 324 (April), 1953.

A review of 973 cases in whom cardiac catheterization was performed revealed that unimportant complications occurred in 264 instances (27.2 per cent), serious accidents in 30 cases (3 per cent), and fatalities in 7 (0.7 per cent). Only in two of the latter could death be attributed to the direct action of the cardiac catheter. In one, a subendocardial hematoma was found near the orifice of the coronary sinus; in the other, a hemopericardium (without other evidence of trauma to the heart or the big vessels).

Acute accidents, apart from the development of arrhythmias, consisted in shock and vasomotor collapse subsequent to febrile reactions in 221 cases (with fatal outcome in two) and acute pulmonary edema in 14 cases (with one death). Late accidents included 47 cases with local infection at the area of insertion of the catheter, 18 cases of thromboembolism, and 13 with pulmonary embolization of which 3 were fatal.

PICK

Scebat, L., Lenègre, J., Ranson-Bitker, B., Benchemoul, F., and Damien, J.: Gas Analysis and Cardiac Output in Various Types of Heart Disease. Arch. mal coeur **46:** 19 (Jan.), 1953.

Oxygen saturations of arterial and venous blood a l calculations of the cardiac index were correl ed with clinical findings in 240 subjects, 12 of w ich had no evidence of heart disease.

n the normal, the values vary within a wide range e ecially the cardiac index (2.52 to 4 liters) and a under the influence of a number of factors, particularly emotional ones, which cannot readily be eliminated in the calculations. In heart disease, especially when well tolerated, the values frequently are close to normal. Pure left heart failure does not significantly change the arterial oxygen saturation even in the presence of marked pulmonary congestion. Combined right and left heart failure leads to venous desaturation and increase of the A-V difference (peripheral desaturation). Heart failure in chronic pulmonary disease is followed by a fall of arterial saturation (pulmonary desaturation) and sometimes by a decrease of the A-V difference.

The cardiac index is definitely low (1.21 to 2.63 liters) in untreated cases of severe combined heart failure. In other and less pronounced types of heart failure, the values are very variable and usually around the lower limits of normal. Hence calculations of the cardiac index, per se, are of no great value in the evaluation of the functional capacity of the heart. However, important information is obtained by correlating cardiac index with auricular pressures, especially in the differential diagnosis of right and left ventricular failure. Conforming with Starling's law, aggravation of heart failure is indicated by divergent alterations of these two values, namely, diminution of cardiac index with increasing pressure in the auricles. Finally the effect of exercise upon the cardiac index should be taken into consideration. The latter will rise in the absence of, and remain unchanged or even drop in the presence of heart failure.

PICK

Scherf, D., Schaffer, A. I., and Blumenfeld, S.: Mechanism of Flutter and Fibrillation. Arch. Int. Med. **91:** 333 (Mar.), 1953.

The different theories of the mechanism of flutter and fibrillation are discussed. Recent conducted experiments are described, which are based on the aconitine method. They demonstrate that these arrhythmias arise from circumscribed tachysystolic centers. The circus-movement theory in any of its forms is unable to account for the findings. A theory of fibrillation is proposed whereby the state of fibrillation is characterized by the presence of innumerable tachysystolic centers of both large and small degree. The theory is based on the presence of minute electrical oscillations in fibrillating muscle. They are small, rapid, and ubiquitous and therefore not manifestations of conducted impulses. They must arise in situ, and they thus constitute tachysystolic foci. Thus there are tachysystolic foci of all sizes throughout the fibrillating myocardium; some are propagated, others remain local.

These tachysystolic centers die out, for the most part, when the sustaining centers are inhibited. The latter are also tachysystolic centers, but they have the ability to maintain themselves for prolonged periods. Fibrillation can be classified accord-

ing to the number of sustaining centers present. Thus, the fibrillation induced by the topical application of aconitine is unifocal, for when the aconitinized site is inhibited the fibrillation stops. On the other hand, faradization or the topical application of acetylcholine results in a multifocal type of auricular fibrillation. To stop fibrillation it is necessary to inhibit several sites. Ventricular fibrillation is a multifocal type, with innumerable sustaining centers which are located probably in the Purkinje fibers. The entire myocardium must be inhibited to stop the fibrillation.

BERNSTEIN

Berte, S. J., and Smith, A. T.: Adams-Stokes Syndrome Due to Ventricular Fibrillation and Tachycardia. New England J. Med. **248:** 282, 1953.

The case of a woman aged 51 years with syncopal attacks followed by convulsions is described. Electrocardiographic observations made during one of the seizures indicated that the attack was due to ventricular fibrillation. The records during normal rhythm showed evidence of prolongation of the P-R and Q-T intervals. These changes and the paroxysmal arrhythmia may all have been due to quinidine sulfate which the patient had been receiving for two days prior to the first seizure. The importance of determining the cardiac mechanism in each case of Adams-Stokes Syndrome before instituting treatment is emphasized.

ROSENBAUM

PATHOLOGY

Wynn, A.: Gross Calcification of the Mitral Valve. Brit. Heart J. **15:** 214 (April), 1953.

The clinical characteristics of 60 individuals with gross calcification of the mitral valve were compared with 120 with mitral valvular disease without gross calcification. Gross calcification is defined as calcification sufficient to be seen by fluoroscopy or the presence of craggy masses of calcareous material at necropsy or mitral valvulotomy. Of the 60 with gross calcification, 48 were recognized radiologically.

The difference was insufficient to be of diagnostic value except that significant mitral incompetence was twice as common in those with gross calcification as in those without it.

SOLOFF

Charan, A.: Diffuse Phlebosclerosis with Calcification. Brit. M. J. **1:** 80 (Jan. 10), 1953.

The author describes a possibly unique case of a 20 year old Hindu who had mammoth calcified superficial venous varices in the arms and legs with a similar abnormality in the head, neck, and renal veins. Renal stone was a concomitant feature difficult to relate to the abnormality of the veins. The possibility of parathyroid dysfunction was eliminated by chemical studies and by surgical exploration of the glands. A congenital basis was suggested by the fact that dilated veins had been noted in the arms and legs soon after birth.

MCKUSICK

PHARMACOLOGY

Hockerts, Th.: The Effect of Digitoxin (Merck) on the Circulation. Cardiologia **22:** 193 (Fasc. 4), 1953.

The author studied in dogs the acute effect of intravenous digitoxin and strophantin K (1/32 to 1/4 mg.) on both the coronary blood flow and on systemic and venous pressure. Rein's "Thermostromuhr" was used as flow meter, and in addition, the arteriovenous oxygen difference of the coronary system was continuously recorded.

In the fully efficient heart of the dog, coronary blood flow remains constant following the injection, but the venous pressure is reduced despite the absence of heart failure. When heart failure was produced by ligation of branches of a coronary artery and the glycosides were injected, the coronary blood flow, cardiac output, and systemic blood pressure increased. These alterations of cardiodynamics were succeeded by augmentation of the oxygen concentration in the coronary venous blood resulting in reduction of the coronary A-V difference. With toxic doses of digitalis, however, both coronary flow and A-V difference became greater. Some possibilities of interrelationship of digitalis effect and cardiac metabolism are discussed.

PICK

Schwartz, S. P., Margolies, M. P., and Firenze, A.: Transient Ventricular Fibrillation. V. The Effects of the Oral Administration of Quinidine Sulphate on Patients with Transient Ventricular Fibrillation During Established Atrioventricular Dissociation. Am. Heart J. **45:** 404 (Mar.), 1953.

Three patients who were subject to recurrent attacks of transient ventricular fibrillation during established atrioventricular dissociation form the basis of this study. The effects of three graded doses of oral quinidine sulfate were studied: (1) 0.2 Gm. given at hourly intervals; (2) 0.4 Gm. given as a single dose; and (3) 0.67 Gm. given as a single dose. Alterations in the cardiac mechanism of the same type occurred in two patients after the use of two hourly doses of 0.2 Gm., and after four hourly doses in the third patient. The drug produced premature beats of the ventricle, periods of asystole following the premature beats, and a prefibrillary mechanism consisting of short runs of fractionated extrasystoles of the ventricles.

After a single dose of 0.4 Gm., bigeminal rhythm appeared with deformed ventricular complexes in which increasingly negative large T waves were interrupted on their ascending limbs by portions of ventricular premature beats. This was followed by a prefibrillary mechanism and then, runs of ventricular fibrillation alternating with a prefibrillary mecha-

nism. These lasted for three and a half hours. The oral administration of a single dose of 0.67 Gm. of quinidine sulfate caused a prefibrillary period within nine and a half minutes, followed by ventricular fibrillation, loss of consciousness and convulsive movements. The mode of recovery was through the appearance of alternate periods of slowing and acceleration of the ventricle.

To sum up, quinidine sulfate depressed ventricular conduction, depressed rhythmicity and irritability, increased the refractory period, and caused recurrent periods of transient ventricular fibrillation that persisted for hours once the mechanism set in following its use. The authors concluded that quinidine sulfate is contraindicated in patients with transient ventricular fibrillation during established atrioventricular dissociation.

RINZLER

January, L. E., Hamilton, H. E., and Sinton, D. W.: Paroxysmal Ventricular Tachycardia Treated with Intravenous Injections of Quinidine. Arch. Int. Med. **91**: 325 (March), 1953.

Eleven patients with paroxysmal ventricular tachycardia received 32 intravenous injections of quinidine for 28 attacks. Twenty-four attacks were terminated abruptly, during, or a few minutes after the injection. In two attacks normal sinus rhythm was not restored for several hours. In two instances there was failure to terminate attacks. One patient died during the injection, but death was not necessarily from quinidine toxicity. It is concluded that under controlled conditions the intravenous use of quinidine is a safe and highly effective means for terminating paroxysms of ventricular tachycardia. It is indicated for the prompt control of ventricular tachycardia in patients who are seriously ill and in patients who cannot tolerate the drug orally.

BERNSTEIN

Weisbert, A., Weinstein, H., and Rosenhaus, H.: Prolonged Ventricular Tachycardia. Arch. Int. Med. **91**: 392 (Mar.), 1953.

The number of cases of myocardial infarction complicated by prolonged and intractable ventricular tachycardia in which the patient survived is almost nil. This case demonstrates the length of time the heart is capable of running a "marathon," so to speak, in spite of massive myocardial infarction.

In case of ventricular tachycardia, certainly, multiple methods of therapy lend themselves to use. Quinidine seems to be the drug of choice, for it is this drug that is of foremost importance in the treatment of ventricular tachycardia in the course of coronary occlusion.

In this case many of the cardiac depressants were used, namely, quinidine, digitalis, procaine amide hydrochloride, and magnesium sulfate. None apparently had any effect on the cardiac rhythm. The heart was almost completely ischemic, highly irritable, necrotic, and incapable of responding to drug therapy simply because its muscular and nervous mechanism was destroyed. Indeed, the heart was actually beating because of its own inherent mechanism and was not controlled by any part of the conduction system.

BERNSTEIN

Malenow, M. R., Batlle, F. F., and Malamud, B.: Prevention of Ventricular Arrhythmias in the Rat by Thyroid Inhibition. Am. J. Physiol. **172**: 743 (March), 1953.

Ventricular arrhythmias were induced by the intravenous injection of calcium chloride solutions. Rats rendered hypothyroid with methylthiouracil were more resistant to calcium injections. These last animals showed a decreased incidence of ventricular tachycardia and fibrillation.

OPPENHEIMER

Shapiro, J. B., and Weiss, W.: Tuberculous Pericarditis with Effusion: The Impact of Antimicrobial Therapy. Am. J. M. Sc. **225**: 229 (March), 1953.

The results obtained in the treatment of tuberculous pericarditis with antimicrobial therapy in 14 patients were compared with those of a control group of 20 untreated patients. The diagnosis was based on the finding of the acid-fast organism in proven cases and on evidence of pericardial involvement obtained by roentgen and electrocardiographic examinations and physical findings. All the treated patients received streptomycin; eight were given PAS and two Isoniazid, in addition. It was found that drug therapy reduced the mortality rate by 50 per cent. Gradual improvement in the roentgen appearance and the electrocardiogram of the treated group was noted; a reduction of fever occurred also in the treated groups. Factors which affected the prognosis unfavorably in both groups were other tuberculous complications, proof of the diagnosis of tuberculosis, and the gradual onset of symptoms. Because of the limited number of cases the authors were unable to outline an optimum therapeutic regimen or to evaluate the longterm result of treatment in tuberculous pericarditis.

SHUMAN

Djordjevic, B. S., Djordjevic-Joksic, M., and Marie, D.: The Circulation Time in Osler's Disease. Arch. mal coeur **46**: 46 (Jan.), 1953.

The lobeline circulation time was determined in 87 cases of subacute bacterial endocarditis with and without evidence of heart failure, and before and after successful treatment.

In cases with heart failure the average value was 19.8 second which is far below the average values (30.2 second) found in other ordinary cases of heart failure. In the absence of heart failure the average circulation time was 9.5 second which in turn is

significantly lower than the normal average values (13.4 second) of the lobeline method reported by others. In a number of cases with healed subacute bacterial endocarditis the average circulation time (30.2 second) corresponded closely to mean values which can be obtained in a series of various types of heart disease.

From this data it seems evident that during the active stage of subacute bacterial endocarditis there is a definite acceleration of the circulation, probably due to alterations of various blood constituents, especially a decrease of the number of red cells and of hemoglobin, and the characteristic alterations of the blood proteins. This deviation from the ordinarily expected circulation time may be of practical importance in the differential diagnosis of bacterial infection of the heart from other types of evolution in chronic valvular diseases.

PICK

Smythe, C. McC., Heinemann, H. O., and Bradley, S. E.: Estimated Hepatic Blood Flow in the Dog: Effect of Ethyl Alcohol on It, Renal Blood Flow, Cardiac Output and Arterial Pressure. Am. J. Physiol. **172:** 737 (March), 1953.

In anesthetized dogs, hepatic blood flow as determined by the bromsulfonphthalein technic, was 29.5 ml. per kilogram per minute (540 ml. per minute). The following parameters were measured after a narcotizing dose of grain alcohol by stomach tube: cardiac output, oxygen consumption, renal blood flow, hepatic blood flow, hepatic bromsulfonphthalein extraction, mean arterial blood pressure, and total hepatic and renal vascular resistance. None of these showed any statistically significant changes after alcohol.

OPPENHEIMER

Cohn, T. D., Cohn, H., and Zuckerman, S.: Paradoxical Response to Carotid Sinus Pressure in Chaotic Heart Rhythm. Arch. Int. Med. **91:** 402 (Mar.), 1953.

An example is presented of a type of chaotic heart rhythm occurring paroxysmally in a young adult. The electrocardiogram, which reveals an unusual pattern of arrhythmias characteristic of a chaotic rhythm, is reproduced and discussed. The electrocardiographic tracing presented no apparent evidence of organic heart disease, and was remarkable in that the runs of fibrillation and flutter were stopped by carotid pressure. Release of the pressure permitted the reestablishment of the abnormal rhythm. This phenomenon is an exception to the accepted rule that only the ventricular complexes of auricular fibrillation and flutter are slowed by carotid sinus stimulation. Hence it tends to indicate that there may be several physiologic mechanisms producing paroxysmal flutter and fibrillation. From the tracing it seems that one of these mechanisms may be similar to that of paroxysmal tachycardia.

BERNSTEIN

Wright, T.: Auricular Tachycardia in Childhood. Brit. M. J. **1:** 25 (Jan. 3), 1953.

Six cases of supraventricular tachycardia in infants aged 4 weeks to 2 years are described. The common clinical picture was that of acute congestive heart failure with an extremely rapid heart rate (200 to 350 beats per minute). The first case responded promptly to neostigmine, 0.125 mg. given intramuscularly, but Digoxin was employed with success in the other cases and is the drug of choice in the writer's opinion. Doses of 0.125 mg. several times daily (by mouth) were well tolerated and seemed to be necessary for recovery. Few of these cases show evidence of congenital heart disease.

MCKUSICK

Siperstein, M. D., Nichols, C. W., Jr., and Chaikoff, I. L.: Effects of Ferric Chloride and Bile on Plasma Cholesterol and Atherosclerosis in the Cholesterol-fed Bird. Science **117:** 386 (April 10), 1953.

The absorption of cholesterol from the intestinal tract requires the presence of bile. Ferric chloride can precipitate bile salts in vitro, and this report shows that the rise in plasma cholesterol, as well as the associated atheromata resulting from cholesterol feeding, can be prevented to a large degree by the feeding of ferric chloride.

It was demonstrated that the feeding of iron, even in the presence of bile, held plaque formation to a degree approximately one-fifth that observed in birds fed cholesterol alone. It was also noted that the feeding of ox bile along with cholesterol results in a greater degree of atherosclerosis and hypercholesterolemia than feeding cholesterol alone. Thus, the enteral administration of ferric chloride reduced the degree of rise of plasma cholesterol in birds fed cholesterol and in those fed cholesterol plus bile. It is probable that iron acts by precipitating bile salts in the intestinal tract.

WAIFE

Best, M. M., Hurt, W. F., Shaw, J. E., and Wathen, J. D.: Study of the Mercurial Diuretic, Dicurin Procaine (Merethoxylline Procaine) by Subcutaneous Injection. Am. J. M. Sc. **225:** 132 (Feb.), 1953.

A unique mercurial compound, forming a chemical combination with procaine base, is Merethoxylline; the new preparation is known as Dicurin Procaine. The diuretic action of this mercurial by subcutaneous administration was compared with that of mercaptomerin sodium (Thiomerin). The effectiveness of these two compounds in promoting diuresis was similar. Some 540 subcutaneous injections were given

to 69 patients with local reactions, including pain, nodule formation, or ecchymosis occurring in 20.3 per cent of the patients following 8.15 per cent of the injections. These reactions were not severe and compared favorably with the incidence of reactions reported elsewhere to Thiomerin. Ecchymosis appeared only in females over 64 years of age and was thought to be due to a local action of the mercury ion since no changes were observed in the blood studies done on these patients. It was concluded that Dicurin Procaine was a satisfactory mercurial compound for subcutaneous use.

SHUMAN

Scheinberg, T., Blackburn, I., and Rich, M.: The Effect of Intravenous Priscoline on Cerebral Circulation and Metabolism. J. Clin. Investigation **32**: 125 (Feb.), 1953.

Priscoline hydrochloride administered intravenously in doses varying from 50 to 100 mg. over a 15 or 20 minute interval resulted in variable effects on cerebral metabolic functions. There was no evidence that Priscoline produces cerebral vasodilatation. Actually a mild cerebral vasoconstriction and slight hypoxia seemed to occur. The apparent clinical effects of Priscoline, attributed to its action on cerebral circulation or metabolism, are difficult to explain on the basis of the results obtained from this study.

WAIFE

Morris, L. E., Noltensmeyer, M. H., and White, J. M. Jr.: Epinephrine Induced Cardiac Irregularities in the Dog During Anesthesia with Trichloroethylene, Cyclopropane, Ethyl Chloride and Chloroform. Anesthesiology **14**: 153 (March), 1953.

The least amount of epinephrine necessary to induce ventricular tachycardia in anesthetized dogs was determined with each of a number of anesthetic agents. The average amount of epinephrine required to produce ventricular tachycardia was 8 gamma per kilogram of body weight with trichloroethylene, 9.7 gamma per kilogram of body weight with cyclopropane, and 8.5 gamma per kilogram of body weight with ethyl chloride. During chloroform anesthesia ventricular tachycardia was not produced by epinephrine injections up to 50 gamma per kilogram of body weight.

SAGALL

Powell, W. F.: Operative Course of Digitalized Surgical Patients. Anesthesiology **14**: 159 (March), 1953.

The operative course of 17 patients who were digitalized was studied. Fifteen patients received Pedilanid during the operative procedure. In 14 patients the operation was performed upon either the cardiac or pulmonary systems. The author believes that 12 patients were improved during the operative procedure. In three, no change was noted, and in two, he was not able to evaluate the results of digitalization. The advantages of intravenous digitalization outweigh the disadvantages.

SAGALL

Sensenbach, W., Madison, L., and Ochs, L.: A Comparison of the Effects of l-nor-Epinephrine, Synthetic l-Epinephrine and U.S.P. Epinephrine upon Cerebral Blood Flow and Metabolism in Man. J. Clin. Investigation **32**: 226 (March), 1953.

Studies of normal healthy males revealed that *l*-nor-epinephrine increases mean arterial blood pressure and reduces cerebral blood flow by virtue of a potent constricting effect on cerebral blood vessels. The cerebral oxygen utilization was not changed. On the other hand, epinephrine administered intramuscularly in doses of from 600 mcg. to 1400 mcg. lowers the mean arterial pressure slightly. It does not affect cerebral blood flow, vascular resistance, or oxygen utilization. The effect on the cerebrovascular metabolism of U.S.P. epinephrine and synthetic *l*-epinephrine is identical.

WAIFE

Loeffler, W., Esselier, E. F., and Foster, G.: Acetyl-Digitoxin, a New Cardiac Glycoside. Schweiz. med. Wchnschr. **83**: 291 (March), 1953.

A new purified glycoside of digitalis lanata, acetyl-digitoxin, was tested in 112 patients with heart failure of various etiologies. The following properties of the preparation were studied in comparison with other digitalis preparations: its pharmacologic and toxic effects, and its effects on clinical manifestations of congestion and on the electrocardiogram.

The new glycoside is generally well tolerated, readily absorbed from the gastrointestinal tract, and acts rapidly. It has a marked slowing effect on the heart rate, a good diuretic effect, and a wide therapeutic range. It can be given orally as well as intravenously with good results even in cases with severe heart failure. It is particularly suitable for rapid digitalization in heart failure with tachycardia due to auricular fibrillation, flutter or paroxysmal auricular tachycardia. Because of its rapid action, it is in these cases even more effective than strophanthin. Signs of overdosage are similar to those caused by other glycosides, and usually disappear from one to three days after discontinuing therapy.

Acetyl-digitoxin has a marked tendency to fixation and is therefore, also suitable for maintenance therapy. Since its effect is more easily reversible, therapy can be better controlled than with digitoxin.

PICK

Rothlin, E., Bircher, R., and Schalch, W. R.: The Pharmacology of Acetyl-Digitoxin-α. Schweiz. med. Wchnschr. **83**: 267 (March), 1953.

Acetyl-digitoxin-α, a chemically defined pure glycoside obtained from lanatoside A, was tested on cats. In chronic subcutaneous and oral medication the effect is protracted but shorter than that of digitoxin. Otherwise the two preparations are very similar in their rapid and intensive action on intravenous application, and in their excellent absorption from the gastrointestinal tract. Overdosage of acetyl-digitoxin produces less vomiting, only minor arrhythmias, and less significant morphologic alterations of the myocardium and the conduction system. Good tolerance, faster disappearing effects and less tendency to cumulation and toxicity are the causes of its wider therapeutic range as compared with digitoxin. Among the typical therapeutic effects the negative chronotropic one is most marked, so that heart failure with rapid heart action seems to be the main indication for the use of the new glycoside.

PICK

Sagall, E. L., and Lewenstein, H. J.: Prolonged Cardiac Pain Following the Intra-Arterial Injection of Priscoline. Report of a Case. New England J. Med. **248**: 278, 1953.

The case of a 63 year old male with a history of hypertension, angina pectoris, and old myocardial infarction is described. A dose of 35 mg. of Priscoline (2-benzyl-4,5-imidazoline hydrochloride) was injected into the femoral artery for treatment of advanced peripheral arteriosclerosis in the corresponding limb. Five minutes after the injection evidence of myocardial ischemia appeared. Electrocardiographic changes appeared and persisted for three weeks. It is assumed that some myocardial necrosis occurred. It is felt that the myocardial damage resulted either from a direct effect of the drug or indirectly as a result of the excessive myocardial demand due to tachycardia, peripheral vasodilatation, or emotion due to the systemic reaction to the drug. The opinion is expressed that since the benefits of intra-arterial administration of Priscoline are uncertain and are outweighed by the potential dangers, this type of therapy should be avoided in patients with known coronary-artery disease. Because coronary atherosclerosis is so common in the older age groups, this form of therapy also is felt to be inadvisable in elderly patients. In the patient described in this report a bilateral common-femoral-vein ligation was done two weeks after the intra-arterial injection. There was evidence of arterial thrombosis at the injection site, a change which was also considered attributable to the intra-arterial therapy.

ROSENBAUM

Laurence, D. R., and Miles, N. A.: Apresoline Intolerance with Bladder Paralysis. New England J. Med. **248**: 464 (Mar. 12), 1953.

The case of a 68 year old woman with mild hypertensive cardiac failure is described. The patient was given Apresoline (1-hydrazinophthalazine hydrochloride) by mouth in doses of 25 mg. every six hours. About 36 hours after the drug was started the patient lost her ability to micturate voluntarily and she did not regain it until 24 hours after the drug was withdrawn, a total of nearly four days. The drug was not withdrawn at once because it was hoped the toxic effects would pass off. Bladder sensation was unaffected. The patient had constipation nausea, vomiting and her first anginal attack during the period of treatment. Subsequent trials of the medication on two occasions resulted in side effects including headache, malaise, weakness, nausea and vomiting, such that the drug had to be abandoned. No difficulty with micturition occurred during these two later trials. The mechanism by which Apresoline is capable of producing bladder paralysis is unknown since the drug is not considered to be a ganglion-blocking agent. Reference is made to one previous report of bladder paralysis due to this drug.

ROSENBAUM

Meitus, M. L., and Wasserman, P.: Influence of Long-Term Bishydroxycoumarin (Dicumarol) Therapy on Liver Function. Arch. Int. Med. **91**: 464 (April), 1953.

Various abnormalities as shown by liver function tests existed in 45 patients who had recieved bishydroxycoumarin (Dicumarol) for two days to 56 months and in 12 persons who had received no bishydroxycoumarin. A comprehensive evaluation failed to disclose marked alteration involving any one specific laboratory procedure, or decided abnormalities, throughout the test of one particular person, to be produced by carefully controlled long-term bishydroxycoumarin therapy. Additional data demonstrated that severe prothrombin deficiency induced by overdosage of bishydroxycoumarin produces toxic liver damage. This damage, evidenced by abnormal findings in the liver function studies, is only temporary and is completely reversible.

BERNSTEIN

Bein, H. J., Gross, F., Tripod, J., and Meier, R.: Experimental Investigations Concerning Hypotensive Effects of Apresoline and Nepresol. Schweiz. med. Wchnschr. **83**: 336 (Apr.), 1953.

Pharmacologic studies are reported concerning the effects of Hydrazinophthalazine (Apresoline) and Dihydrazinophthalazine (Nepresol). Both compounds produce in various animal species a protracted fall in blood pressure, associated with increases of the heart and respiratory rates. A persistent increase of blood flow in the visceral organs,

especially in the mesenteric and renal arteries, supports the view that the drop in blood pressure is due to a decrease of the total peripheral resistance. However, no definite effect on cardiac output could be found in the experiments. Both drugs have a partial sympatholytic effect which, however, is not the principal factor in the lowering of the blood pressure. Hypertension produced by pitressin or renin is not relieved in contrast to that produced by serotonin. Apresoline increases the sensitivity to veratrin; it weakens the carotid sinus reflex, and lowers hypertension due to anoxia. The usual hypertension subsequent to electric stimulation of the afferent stump of the vagal or ischiadic nerve does not occur following Apresoline medication.

The authors conclude that the hypotensive action of Hydrazinophthalazine is due to a complex mechanism, effected partly by a direct action on peripheral vasomotors and partly initiated over central nervous regulations.

PICK

PHYSIOLOGY

Alman, R. W., and Fazekas, J. F.: Apparatus for Continuous Blood-Pressure Observation. New England J. Med. **248:** 105, 1953.

A method is described for continuous observation of the mean arterial blood pressure. The apparatus employs an aneroid manometer attached by means of a short rubber bushing and a 2 cc. syringe barrel to a three-way stopcock. A 5 or 10 cc. syringe filled with sodium citrate or heparinized saline serves as a reservoir. An indwelling arterial needle is attached to the stopcock outlet. The pressure chamber is filled from the reservoir until the manometer registers a level higher than the anticipated mean arterial blood pressure. When arterial puncture is made, the compressed air in the manometer and pressure chamber forces fluid into the tubing and into the artery until pressure equilibrium is reached. The apparatus is said to make continuous observation of the blood pressure simple and automatic. It requires little attention; it is simply contrived, easily maintained and sterilized, and not subject to breakage. Arterial puncture is required and occlusion or dislodgement of the needle may interrupt its continued use.

ROSENBAUM

Rushmer, R. F., Crystal, D. K., Tidwell, R. A., and Hendron, J. A.: Cinefluorographic Studies of Cardiovascular Disease. Am. J. Roentgenol. **69:** 385 (March), 1953.

The authors describe an improved method of photographing fluoroscopic images on 16 mm. film and discuss the application of this method as a diagnostic tool. It is possible to visualize angiocardiographic densities within the heart shadow. The maximal exposure to the patient is limited to 20 roentgens, an exposure time roughly equivalent to one minute of fluoroscopy.

SCHWEDEL

Venner, A., and Holling, H. E.: Comparison of Operation and Clinical Findings in Mitral Stenosis and Incompetence. Brit. Heart J. **15:** 205 (April), 1953.

Of 96 individuals subjected to mitral commissurotomy, 61 were regarded by the surgeon as having pure mitral stenosis, 26 mitral stenosis and regurgitation, and 9 predominant mitral regurgitation.

No significant difference could be detected in the first and third group by clinical, radiologic, or electrocardiographic studies or by the results of cardiac catheterization. A snappy first sound and a tapping cardiac impulse is more common in stensois and an absent tapping impulse more common in regurgitation, but even here overlapping is present.

If the clinical situation favors surgery, surgical exploration of the valve is indicated where the condition of the valve is uncertain.

SOLOFF

Taran, L. M., Gulotta, G. A., Szilagyi, N., Jablon, J. M., and Lane, W. K.: Effect of Cortisone and ACTH on the Protracted Phase of Rheumatic Carditis in Children. Am. J. Med. **14:** 275 (March), 1953.

All 16 children with protracted rheumatic carditis showed clinical improvement while they received cortisone or corticotropin (ACTH). When this therapy was discontinued, they again demonstrated clinical and laboratory evidence of rheumatic carditis. None of the patients showed regression in clinical evidence of endocarditis or cardiac hypertrophy. Cortisone and corticotropin seem to "damp" the symptomatology in protracted carditis only during the period when the hormone is administered. Many of the patients exhibited some untoward effects. Whether this form of therapy significantly affects the course of rheumatic disease in cases of long standing remains to be proven.

HARRIS

Mathieu, L., Grilliat, J. P., and Pillot, P.: Variations of the Residual Air in the Course of Mitral Stenosis. Arch. mal. coeur **46:** 341 (April), 1953.

The authors studied the respiratory dynamics in 20 cases of mitral stenosis and were able to distinguish three groups. The first consisted of patients with good compensation in which there was a reduction of the total lung capacity, affecting equally the vital capacity and the residual air. In cases with congestive heart failure, which formed a second group, there was no apparent disturbance of the total lung capacity since a reduction of vital capacity was associated with some increase of the residual air. Less consistent findings were present in

a third group. However, a frequent finding here was a decrease of the index of Tiffeneau relating ventilation on exercise to lung volume. In association with a marked increase of the residual air this suggests secondary bronchial disease developing subsequent to the disturbance of cardiodynamics by mitral stenosis.

PICK

Donzelot, E., Dubost, Ch., Heim de Balzac, R., Metianu, C., and Gallemot, K.: Recurrence of Mitral Stenosis Following Comissurotomy. Arch. mal. coeur **46:** 301 (April), 1953.

The authors report the case of a 29 year old woman who underwent mitral finger fracture valvulotomy for severe mitral stenosis with progressive course and heart failure. Following considerable initial clinical improvement, a typical diastolic rumble reappeared at the apex on the fifteenth postoperative day, and concomitantly increasing dyspnea and signs of right heart failure—all suggesting a recurrence of the mitral stenosis. The patient died after a rapid downhill course, one month after surgery. Autopsy revealed an adhesive pericarditis in organization, and an auricular thrombus adherent to the area of the fractured mitral valve at the lateral commissure. Here, the mitral leaflets were sealed together by a recently developed valvular scar. The auricular wall and the mitral leaflets showed histologic evidence of recent and old inflammation. The localization of the auricular thrombus in the area of fracture suggests that the process of organization of this thrombus involved the mitral opening resulting in its reclosure. This probably occurs to some extent commonly following mitral surgery, especially in the presence of active endocarditis, but the remaining aperture of the ostium usually is sufficient to maintain the improvement achieved by the operation.

PICK

Turchetti, A.: Clinical and Radiologic Features Particular to Mitral Disease. Acta cardiol. **8:** 111 (Fasc. 2), 1953.

The author discusses alterations of pulmonary hemodynamics in mitral stenosis. An important factor appears to be vascular tone which is variable from patient to patient. Increased vascular tone may compensate for the lesion, first by elevation of pulmonary venous pressure and later by the development of pulmonary arterial hypertension. Both alterations tend to maintain a sufficient pressure gradient between different portions of the pulmonary circulation, which is necessary to overcome the obstacle at the valve. An insight into the complexity of these conditions can be gained with the help of cardiac catheterization, and tomographic visualization of the pulmonary veins following an artificial pneumomediastinum.

Variations of these pressure relationships can explain the individual variations of symptoms and signs in mitral stenosis, for instance the tendency to acute pulmonary edema and/or hemoptysis in some patients, and the development of morphologic vascular changes, or anginal pain in others. The distinction of organic from functional alterations of the pulmonary circulation based on the evaluation of these clinical manifestations of the lesion is of value in the selection of cases suitable for surgery

PICK

Coelho, E., Fonseca, J. M., Nunes, A., and Rocha Pinto: Arteriography of the Coronary Circulation in Man. Cardiologia **22:** 45 (Fasc. 1), 1953.

The authors report their experience in the visualization of normal and pathologic coronary arteries with the help of retrograde arteriography. In preliminary experiments on dogs a catheter was introduced through one of the carotid arteries into the aorta, and following injection of the dye both coronaries were clearly delineated with their ramifications. The experiments were repeated after production of myocardial infarction by ligation of the anterior branch of the left coronary. The coronary angiogram showed a distinct stop at the point of the lesion.

The method was then successfully, and without accident, used in a number of patients. The catheter was introduced through the radial artery and advanced to the level of the coronary ostia. The best results were obtained with injection of 50 to 60 cc. of 20 per cent Diodrast within four to five seconds, with manual compression of the carotid arteries at the moment of injection. The coronary arteries were seen in their entire course and both anomalies of their branching and pathologic alterations in their lumen and walls could be visualized. Representative illustrations are shown and the value of the method in the diagnosis of coronary artery disease is pointed out.

PICK

Elisberg, E. I., Miller, G., Weinberg, S. L., and Katz, L. N.: The Effect of the Valsalva Maneuver on the Circulation. II. The Role of the Autonomic Nervous System in the Production of the Overshoot. Am. Heart J. **45:** 227 (Feb.), 1953.

Further data on the mode of action of the autonomic nervous system on the Valsalva maneuver was sought by observing the changes in venous pressure simultaneously with those of arterial pressure and heart rate in normal individuals, and by noting the alterations in response after atropinization and tetraethylammonium chloride. Tetraethylammonium chloride prevents the usual overshoot and bradycardia by blocking vasopressor reflexes during and immediately after sustained straining. Atropine blocks the parasympathetic nervous system and the overshoot is exaggerated and prolonged while the bradycardia is abolished. Venous pressure rises in a similar manner during straining, even after

the administration of tetraethylammonium chloride or atropine.

RINZLER

Walser, M., Seldin, D. W., and Grollman, A.: An Evaluation of Radiosulfate for the Determination of the Volume of Extracellular Fluid in Man and Dogs. J. Clin. Investigation **32**: 299 (April), 1953.

Intravenous radiosulfate (S^{35}) was found to be a satisfactory and convenient measure of the "functional extracellular fluid volume" in normal man and dogs. A diffusion equilibrium after a single injection was achieved in from 15 to 20 minutes in man. Only 4 to 8 per cent of the dose is excreted during this time. Cellular penetration was slight and half the dose was excreted within four to nine hours. Repeated determinations in a single individual differ by an average of only 0.16 to 0.30 liters. In relation to the simultaneously determined inulin space the ratio of radiosulfate was found to be 0.95 ± 0.11. In 28 normal men and women the radiosulfate space averaged 15.1 per cent of the body weight.

WAIFE

RHEUMATIC FEVER

Kaltman, A. J., Schwedel, J. B., and Straus, B.: Chronic Constrictive Pericarditis and Rheumatic Heart Disease. Am. Heart J. **45**: 201 (Feb.), 1953.

The clinical pictures of five patients with rheumatic heart disease and chronic constrictive pericarditis are presented in detail. These cases were gathered from a total of 18 cases of constrictive pericarditis, all proved by operation or autopsy. The authors point out, on the basis of this experience, that cardiac enlargement, normal intensity of heart sounds, and normal cardiac pulsations are not rare in patients with constrictive pericarditis, and that this diagnosis should be suspected in patients with heart disease who have an atypical course.

RINZLER

Weinstein, L.: Group A Polysaccharide Precipitin Reactions in Acute Streptococcosis and Rheumatic Fever. Yale J. Biol. & Med. **25**: 349 (April), 1953.

The study was based upon 537 patients with a variety of infectious diseases, technical methods being given in detail. Positive precipitin reactions against the group specific carbohydrate, or C substance, were obtained in one third of the cases of scarlet fever and one fourth of the cases of acute rheumatic fever. Most striking was the finding that not all of the patients with proved streptococcal infection developed a precipitating antibody for the carbohydrate. This may be a consequence of the relatively poor antigenicity of the polysaccharide. Furthermore, a relatively high incidence of anti-C antibody was found in a number of infectious diseases unrelated to streptococcus, including chicken pox, scabies, and syphilis. It is therefore stressed that absence of anti-C antibody does not exclude active streptococcic disease or rheumatic fever, nor does the presence of the antibody prove the existence of streptococcic infection. The findings also tend to minimize the role of sensitization to group-specific streptococcal polysaccharide as a mechanism in the development of the rheumatic state.

ENSELBERG

SURGERY IN HEART AND VASCULAR SYSTEM

Stephen, C. R., Nowill, W. K., and Martin, R.: Diagnosis and Treatment of Hypotension During Anesthesia. Anesthesiology **14**: 180 (March), 1953.

Hypotension occurring during anesthesia should be recognized promptly and therapy instituted to prevent serious and disastrous sequellae. Logical therapy requires the proper assessment and alleviation of the etiologic factors. A variety of mechanisms may produce hypotension during anesthesia. These include the development of myocardial infarction, hemorrhage, drugs used in premedication, anoxia, the rapid introduction of anesthetic drugs into the blood stream, the rapid induction of ether or cyclopropane anesthesia, spinal anesthesia, celiac plexus reflex stimulation, excessive vagal stimulation, traction on various abdominal organs, injection of dye into the carotid artery, and surgical repair of arteriovenous fistulas. The authors present cases illustrating the above factors and discuss the management in each case.

SAGALL

Moore, H. D.: Ligation of the Popliteal Vein for the Gravitational Syndrome. Lancet. **1**: 23, (Jan. 3), 1953.

Patients were selected for operation on the basis of absence of demonstrable valves in the deep veins of the leg on venography. Popliteal ligation was performed in order to interrupt the unsupported column of blood from heart to feet. Complete relief of symptoms—ulceration, aching, edema—was achieved in 18 of 23 legs so treated.

MCKUSICK

Zipf, H. F.: The Elimination of Cardiac Sensibility by Local Anaesthetics in Cardiac Surgery. Klin. Wchnschr. **31**: 79 (Feb.), 1953.

Following a review of methods used in cardiac surgery for anesthesia of the heart and the pericardium, and their various physiologic and pharmacologic effects upon the circulation, the author presents the result of his own animal experiments with various compounds, related to p-Aminosalicylic acid and having local anesthetic effects. In cats a number of such drugs were applied directly to the heart, or injected intravenously either in a single

dose or in protracted form as infusion. Action potential of afferent cardiac fibers of the vagus were recorded together with the electrocardiogram and the pneumogram. A decrease in the number of "pain impulses" in the vagus nerve was used as a measure of the efficiency of an anesthetic.

A single intravenous injection of an anesthetic is less effective than a protracted intravenous infusion in suppressing afferent cardiac impulses, however, toxic effect upon the myocardium occurs with both as is evident from contour changes in the electrocardiogram. Direct infiltration of the heart is as equally effective as intravenous application. Instillation into the pericardial cavity produces only partial anesthesia of limited duration, not sufficient for completion of an operation. Oxycain gave better results on local application than procain. Rheonocain proved most powerful for intravenous anesthesia but was two to four times more toxic than the other compounds. The usefulness of these experimental results in clinical instances remains to be tested.

PICK

Pierce, V. K., Boyan, C. P., and Masterson, J. G.: Studies on Venous Blood Pressure in Patients Undergoing Major Surgical Procedures. Surg., Gynec. & Obst. **98:** 310 (Mar.), 1953.

The authors studied venous blood pressure in 60 patients subjected to major operative procedures, in order to determine whether the readings were more sensitive than arterial blood pressure in detecting impending shock. The usual type of apparatus was used.

In all cases blood loss was associated with a significant fall in venous pressure. This change preceded the reduction in arterial pressure and the increase in pulse rate. It was therefore concluded that venous pressure readings were more sensitive than the other two measurements in evaluating operative blood loss and the degree of surgical shock when this state was in evolution.

ABRAMSON

Jordan, P., Jr., Hiertonn, T., and Johnston, C. G.: Arterial Replacement in Trauma. Am. J. Surg. **85:** 424 (March), 1953.

Using dogs the authors studied the changes produced in aortic segments obtained from donors and placed in recipients. The arterial grafts were first either lyophilized or preserved in Tyrode's solution for varying periods of time.

The patency rate of such arterial grafts was found to be high, the period of observation being six months. Histologically the segments showed replacement by the host tissues. Rapidly frozen lyophilized grafts were considered to be superior to the slowly-frozen segments, since no disruption of cells due to the formation of macrocrystals was noted in the former.

It was concluded that lyophilization of blood vessels could solve the problem of maturing, which is the greatest single deterrent in present-day methods of vascular graft preservation and banking.

ABRAMSON

James, A., Coulter, R. L., and Saunders, J. W. Controlled Hypotension in Neurosurgery, with Special Reference to Hypotension Induced by Pneumatic Suction Applied to the Legs. Lancet **1:** 412, 1953.

The combination of either suction to the legs or posture with hexamethonium decreased the amount of drug necessary and the duration of postoperative hypotension. Blood pressure could be controlled at will by varying suction pressure. The decrease of bleeding and reduction of intracranial tension permits a higher standard of neurosurgery with reduced mortality, transfusions, and duration of anesthesia. Complete removal of vascular masses was facilitated. Pressures of 55 to 65 mm. Hg were employed to reduce bleeding. Although no untoward effects on the coronary circulation were observed in 150 operations, electrocardiographic observations during operation are recommended in doubtful cases.

MCKUSICK

Van Bogaert, A., Fannes, E., Buytaert, L., De Munck, J., Van Genabeck, A., Van der Henst, H., and Vandael, J.: Pulmonary Arterial Hypertension Following Ligation of One or More Pulmonary Veins. An Experimental Study. Arch. mal. coeur **46:** 289 (Apr.), 1953.

Acute simultaneous ligation of one to three pulmonary veins of one lung, with the pulmonary artery and the main bronchus left intact, produced in dogs sudden pressure elevation in the pulmonary artery of the same as well as the contralateral lung. On one occasion this was followed by the development of pulmonary edema. Upon relief of the venous constriction the pulmonary arterial pressure returned to normal levels.

These experimental findings are discussed with respect to pulmonary hypertension found in mitral stenosis. Labile hypertension can be caused by a reflex constriction of pulmonary arterioles subsequent to distension of the entire, or parts of, the pulmonary venous bed. This hypertension may be considered a protective mechanism which prevents instantaneous disturbances of the pulmonary circulation by regulation of blood flow to the involved areas. The presented observations provide experimental proof for this mechanism hypothesized previously by others on the basis of clinical observations in mitral disease. This mechanism however cannot account for persistent pulmonary hypertension, in which, probably, some additional pressure-maintaining factors may come into action.

PICK

Kaufman, H., Ross, A., Bernhard, V. M., Bourdeau, R. V., Furr, W. E. Jr., and Douglass, T. C.: Graded Hepatic Arterial Ligations in Experimental Ascites. Surg., Gynec. & Obst. **96:** 409 (April), 1953.

The authors studied the effect of various degrees of hepatic arterial deprivation on mechanically induced ascites in 41 dogs. In 10 control animals partial constriction of the inferior vena cava in the thorax was produced using an aluminum band, while in 13, this procedure was combined with limited hepatic arterial ligation. In the remaining 18 dogs, massive arterial deprivation of the liver was carried out in conjunction with the thoracic caval obstruction.

The results indicated that ascites accumulation could not be prevented when only the hepatic artery was ligated. On the other hand, when the main arterial supply was severed, ascites did not form. The evidence, therefore, suggested that within certain limits, the more extreme the arterial deprivation of the liver, the better was the protection against the formation or reformation of ascites. However, the greater the arterial deprivation, the higher was the mortality.

ABRAMSON

THROMBOEMBOLIC PHENOMENA

Woesner, M. E., Gardiner, G. A., and Stilson, W. L.: Pulmonary Embolism Does Not Necessarily Mean Pulmonary Infarction. Am. J. Roentgenol. **69:** 380 (March), 1953.

This consists of a report of a dyspneic and cyanotic male in whom the following characteristics of pulmonary artery embolism occurred without subsequent pulmonary infarction: abrupt termination of a major arterial branch at the site of the embolus; increased radiolucency and absence of the fine reticular vascular pattern in the lung roentgenogram; and dilatation of the pulmonary artery proximal to the embolus.

The source of the emboli was in a popliteal vein, where old as well as recent thrombosis had occurred. The right heart chambers were hypertrophied and dilated; clinically he was in right heart failure.

SCHWEDEL

Oppenheimer, M. J., Durant, T. M., and Lynch, P.: Body Position in Relation to Venous Air Embolism and the Associated Cardiovascular-Respiratory Changes. Am. J. M. Sc. **225:** 362 April), 1953.

The left lateral position has been recommended by the authors as a means of treating venous air embolism because of the location of the obstructing air trap located in the right ventricular outflow tract with the patient on his back or right side. In the left lateral position the air trap is displaced into the right auricle or ventricle as the right ventricular outflow tract is located inferiorly. This thesis was studied in a series of venous air embolism animal experiments. With doses of injected air of 7.5 cc. per kilogram the chances of survival of the animals were doubled with the animal in the left-side-down position compared to the supine or right-side-down position. Turning the animal to the favorable position within one minute after injection was equally good.

Immediately following air injection, there was an abrupt rise in pulmonary arterial pressure and a fall in systemic pressure. There was an associated bradycardia due to abortive beats which failed to open the aortic valve. The pulmonary venous pressure was elevated in many of the experiments. The respiratory pattern was that of hyperpnea followed by apnea and then polypnea for a longer period. It is suggested that the changes observed depend on reflexes from the heart and pulmonary vessels and on mechanical factors.

SHUMAN

Glas, W. W., Grekin, T. D., and Musselman, M. M.: Fat Embolism. Am. J. Surg. **85:** 363 (March), 1953.

A series of 109 patients suffering from moderate or serious injuries was studied to determine the incidence of fat embolism. Of the group, 52 per cent were found to be suffering from this condition. Pulmonary and cerebral symptoms were common, these being considered to be due to the existing condition.

On the basis of their findings, it was the authors' opinion that fat embolism is a disorder of great importance and of relatively frequent occurrence. The diagnosis should be suspected in every patient who has been injured and who exhibits characteristic clinical manifestations for which no other cause can be demonstrated. The presence of fat globules in the urine and the sputum is of importance in determining the presence of the condition. The pathogenesis of fat embolism is not clear.

ABRAMSON

Richards, R. L.: Thrombo-angiitis obliterans. Clinical Diagnosis and Classification of Cases. Brit. M. J. **4808:** 478 (Feb. 28), 1953.

The author calls attention to the fact that there is no unanimity regarding the criteria necessary to differentiate thromboangiitis obliterans from arteriosclerosis obliterans. Because of this, he reviews the case histories of 85 patients with a clinical diagnosis of thromboangiitis obliterans. Only one was of Jewish extraction. Superficial migratory thrombophlebitis occurred in 32 per cent of the cases, while in 29 per cent there was clinical evidence of involvement of the arteries of the upper limbs. The patients were divided into several categories. In the "acute" group, the disease began suddenly or

insidiously and progressed rapidly, gangrene forming within a year of onset. In the "episodic" group, there was a history of a series of episodes of thrombosis, either arterial or venous, with quiescent periods intervening. In the "slowly progressive" category, intermittent claudication was the chief complaint, while trophic changes were late manifestations. In the "acute arterial occlusion" group, the onset was sudden, indicating that thrombosis of either the femoral or popliteal artery had occurred.

With the possible exception of superficial migratory thrombophlebitis, none of the clinical features of thromboangiitis obliterans was considered to be pathognomonic. According to the author, the diagnosis was often dependent upon the natural history of the patient's illness. Two findings which were believed to be of value as differential points were the constant association of the disease with tobacco smoking and its predilection for the male sex.

ABRAMSON

Fulton, G. P., Akers, R. P., and Lutz, B. R.: White Thrombo-embolism and Vascular Fragility in the Hamster Cheek Pouch after Anticoagulants. Blood **8:** 140 (Feb.), 1953.

Heparin, Dicumarol, Tromexan, and Phenylindanedione did not prevent but actually enhanced, the formation of platelet plugs at the site of hemorrhages produced at the tip of a stimulating microelectrode in contact with the walls of small blood vessels in the hamster cheek pouch. Furthermore, these anticoagulants, per se, produced an increased adhesiveness of platelets and leukocytes to the endothelium of small venules. The significance of increased platelet agglutinability during the hypocoagulable state induced by anticoagulants, and the need for a critical distinction between agglutinability of the formed elements and coagulation involving fibrin are discussed.

An increase in the fragility of the walls of venules followed the administration of heparin, Dicumarol, Tromexan, and Phenylindanedione. A brief series of relatively weak faradic shocks from a microelectrode produced a hemorrhage. Shocks of much greater strength applied to venules of normal untreated hamsters produced no visible effect. This method is proposed as a new semiquantitative procedure for investigation of vascular fragility in accessible membrane preparations. It may possibly distinguish between fragility in the sense of rhexis or breaking of the wall, and petechial formation such as that produced by the application of negative pressure and perhaps erroneously referred to in the literature as "fragility."

BERNSTEIN

Davis, H. A.: Studies in Thrombo-embolic Disease: I. Acute Early Pulmonary Embolism (within forty-eight hours) Following Surgical Operation, Trauma and Hemorrhage. Ann. Surg. **137:** 356 (March), 1953.

The author presented a study of 22 clinical cases in which acute pulmonary thromboembolism took place within 48 hours following surgical operation, accidental injury, or hemorrhage. Most of the patients were 50 years of age or more. In each instance death occurred and the diagnosis was confirmed by postmortem examination. The majority of the emboli arose from the veins of the lower extremities. There was a high incidence of antecedent shock and hypotension in the series. No relationship could be established between the extent of trauma and the acute rapidly developing form of pulmonary thromboembolism.

On the basis of the data obtained from the study, it was concluded that antecedent shock appeared to be a significant etiologic factor in this disease.

ABRAMSON

Clatworthy, H. W., Jr., Dickens, D. R., and McClave, C. R.: Renal Thrombosis Complicating Epidemic Diarrhea of the Newborn. Nephrectomy with Recovery. New England J. Med. **248:** 628, 1953.

The patient reported was 1 of 10 infants in a nursery for the newborn who were afflicted simultaneously with severe diarrhea. Some evidence of renal involvement in addition to the usual signs and symptoms of epidemic diarrhea was noted in each case. The patient reported developed diarrhea due to *Escherichia coli* Type 0 111, B_4 at three days. On the fifteenth day of life a mass appeared in the left flank. Left nephrectomy was carried out successfully on the nineteenth day of life with subsequent normal progress.

It is pointed out that renal thrombosis is only one of the severe intravascular complications frequently seen in infants. However, renal thrombosis occurs rarely in infants except as a complication of epidemic diarrhea of the newborn. Although the cause of such intravenous coagulation is unknown, stasis of blood due to decreased blood volume, hemoconcentration, and arteriolar constriction probably play roles. Gross hematuria is less often present than not in these patients. The appearance of a mass in the region of one or both kidneys should suggest the diagnosis, and intravenous pyelography is often very helpful in the differential diagnosis. Results of removal of the involved kidney when infarction is unilateral are usually very satisfactory.

ROSENBAUM

VASCULAR DISEASE

De Marneffe, R.: Facts Concerning Bone Vascularization in Paget's Disease. Acta Cardiol. **8:** 181 (Fasc. 2), 1953.

An anatomic and histologic study of bones affected by Paget's disease revealed vascular alte a-

ions, consisting in proliferation of the media and intima of bone arteries, and causing a diminished arterial flow. However, no direct communication between an artery and vein could by demonstrated. It is therefore concluded that, "if the arterialization of venous blood in an extremity of a patient with Paget's disease is considered evidence of an arteriovenous shunt, the morphologic evidence is lacking that this shunt occurs within the affected bone."

PICK

Guy, C. C., and Wichowski, W. A.: Rupture of Blood Vessels by Strenuous Physical Exertion. Am. J. Surg. **85**: 418 (March), 1953.

The authors presented three typical cases of rupture of blood vessels due to severe physical exertion and reviewed the literature on this subject. It was their belief that pre-existing disease of the involved structure was not a necessary prerequisite for the production of this abnormality. The most common example of such a response was found to be rupture of the epigastric vessels, usually with physical strain, in women who were or had been pregnant. In the case of the extremities, the characteristic changes were a hard tender swelling, followed by the appearance of hemorrhagic discoloration in the distal portion of the limb several days later.

ABRAMSON

Stevenson, F. H.: Infected Arteriovenous Fistula in the Lung. Lancet **1**: 626 (March 28), 1953.

The patient, a 58 year old man, had multiple telangectasia with an arteriovenous fistula of the right middle lobe and developed a clinical picture consistent with infection of the fistula by *Staphylococcus pyogenes*, which was cultured from the blood. Cure was effected with penicillin and aureomycin.

MCKUSICK

Meneely, J. K. Jr., and Bigelow, N. H.: Temporal Arteritis. A Critical Evaluation of this Disorder and a Report of Three Cases. Am. J. Med. **14**: 46 (Jan.), 1953.

The authors summarize the syndrome of temporal arteritis and report three new cases, one of which was fatal. They recommend that the term, temporal arteritis, should be restricted to instances in which the affected vessel has undergone the characteristic granulomatous changes associated with foreign body giant cells. They prefer the use of the pathologic term, granulomatous arteritis. This syndrome is characterized by severe headaches, pain in the temporal region, and the presence of inflamed, thickened, and tortuous temporal arteries. Constitutional symptoms of a generalized infection are also present. The characteristic pathologic lesion consists of proliferation of inflamed fibrous tissue of all layers of the affected vessel, together with focal necrosis and granulomatous lesions associated with foreign body giant cell formation in the media. Good therapeutic results are obtained by procaine injection, surgical excision of a portion of the diseased vessel and, in at least one instance, antihistamine therapy. The disorder is usually self-limited and nonfatal. Although this condition is generally a localized vascular disease of the temporal arteries, other cranial arteries, as well as arteries in other parts of the body, may show the same type of lesion.

HARRIS

Betts, J. W., and Rowlands, B. C.: Leaking Abdominal Aneurysms. Two Unusual Cases. Brit. M. J. **1**: 73 (Jan. 10), 1953.

Two patients are described who presented tender, irreducible swelling in the inguinal area. In each case incarcerated hernia with strangulation was the tentative diagnosis. In each case operation and necropsy revealed large arteriosclerotic aneurysms of the aortic bifurcation area with rupture into the retroperitoneal area.

MCKUSICK

Boyce, W. H., Detar, J. H., and Vest, S. A.: A New Technique of Venography of the Lower Extremities with Urokon. Surg., Gynec. & Obst. **96**: 471 (April), 1953.

A new method of venography is described for visualization of the large veins of the lower extremity. The contrast material is buffered with 70 per cent Urokon sodium which has a relatively high specific gravity, as compared to whole blood. This physical property causes the dye to gravitate into the dependent venous system to the level of competent valves.

In the male the material is injected into the superficial dorsal median vein of the penis. If immediate x-ray exposure fails to show filling of the iliofemoral systems on both sides, a second exposure is made following another injection of the contrast medium into the superficial lateral vein of the penis, on the side which failed to be visualized. In the female the material is injected into the superficial circumflex iliac or any other superficial vein which empties into the saphenous or deep femoral vein in the thigh. In order to obtain bilateral filling, vessels on both sides have to be injected.

The advantage of the proximal injection technic is its simplicity. Furthermore, it requires no special equipment, local anesthesia, or physical exertion on the part of the patient. With this method, the main trunk of the profunda femoris vein will be visualized, a feat which cannot be consistently duplicated by any procedure involving distal injection.

ABRAMSON

Bahnson, H. T.: Definitive Treatment of Saccular Aneurysms of the Aorta with Excision of Sac and Aortic Suture. Surg., Gynec. & Obst. **96**: 383 (April), 1953.

The author reports the results of surgical treatment of eight patients with saccular aneurysms in different portions of the aorta and reviews the literature on this subject. In six of his cases excision of the sac and suture of the aorta were successfully carried out. It is his belief that resection of saccular aneurysm with preservation of aortic continuity is feasible in all regions of the aorta.

ABRAMSON

OTHER SUBJECTS

Peschel, E., and Lohmann-Peschel, R.: Electrolyte Metabolism During Rice Diet. (Serum Electrolytes in Patients with Severe Primary or Secondary Renal Disease.) Arch. Int. Med. **91:** 296 (Mar.), 1953.

A study was made on 80 patients with severe primary or secondary kidney disease in regard to the tolerance to a rigid restriction of sodium chloride intake, as in the rice diet. The degree of impairment of kidney function was characterized by an average initial blood nonprotein nitrogen of 77 mg. per 100 cc. and an average phenolsulfonphthalein excretion of 22 per cent. The period of time on strict rice diet until major electrolyte distrubances developed was used as a criterion for the tolerance to the rigid restriction of sodium chloride intake. It was found that in this series of patients 45 per cent did not show a major electrolyte disturbance after three months on strict diet, 7.5 per cent showed it after three months, 18.8 per cent after two months, 17.5 per cent after one month, and 7.5 per cent after half a month; 3.7 per cent were in major electrolyte imbalance before the diet (in modified form) was started.

There was no distinct correlation of these findings with the nature of the processes which led to the renal insufficiency. The deficiency in renal electrolyte conservation could be compensated for by astonishingly small additions of sodium chloride if these were given early enough, so that even with the modifications, the diet could be kept well within the range of a very low sodium diet. Acidosis did not occur, although the general clinical state of many of these patients would have led one to expect its presence. The composition of the rice diet helps to reduce the production of acid radicals and favors the formation of bicarbonate reserve.

BERNSTEIN

Hustin, A.: A Cardio-Tachograph. Acta cardiol. **8:** 166 (Fasc. 2). 1953.

An electric device is described for direct recording of the instantaneous or average heart rate. The R waves of the electrocardiogram are amplified and changed to signal waves, which are counted by a system of condensators and recorded on paper moving under visual control. All other deflections, including artefacts, regardless of their size, are eliminated so that the apparatus can be used with the patient moving around.

PICK

Schwartz, W. B., and Relman, A. S.: Metabolic and Renal Studies in Chronic Potassium Depletion Resulting from Overuse of Laxatives. J. Clin. Investigation **32:** 258 (March), 1953.

Studies were carried out on two women who had gradually developed severe potassium deficiency as a result of chronic diarrhea induced by overuse of laxatives. There were no neuromuscular symptoms and signs, but there were T-wave changes suggestive of hypokaliemia on routine electrocardiogram. The renal excretion of potassium was very low. The serum showed no other significant disturbance except for a slight elevation of plasma bicarbonate in one of the two patients. The sodium, potassium, and phosphorus concentrations of the red cells were normal. The ability to concentrate urine was impaired prior to treatment but was restored to normal by correction of the potassium deficit. It is believed that the very slow rate of potassium loss was responsible for the absence of significant signs and symptoms.

There was also found to be a very close correlation between total exchangeable potassium and the potassium balance. This observation implies that exchangeable potassium measures the metabolically active pool of potassium in the body whether or not it measures total body potassium.

WAIFE

Epstein, F. H., Post, R. S., and McDowell, M.: The Effect of an Arteriovenous Fistula on Renal Hemodynamics and Electrolyte Excretion. J. Clin. Investigation **32:** 233 (March), 1953.

Because opening or closing an arteriovenous fistula causes an immediate and marked change in peripheral resistance and numerous compensatory adjustments, it was of interest to study renal physiology in 17 male casualties of the war with large arteriovenous fistulas. It was found that occlusion of an established fistula results in an increased excretion of sodium by the kidney. This is accompanied by the well-known rise in diastolic pressure and bradycardia, although there was no change in glomerular filtration rate, renal blood flow, or renal venous pressure. Changes in sodium excretion in different patients could not be correlated with the magnitude of blood pressure response, and the data suggest that renal excretion of sodium may be conditioned by the degree of filling of some portion of the arterial tree.

WAIFE

Le Quesne, L. P., and Lewis, A. A. G.: Postoperative Water and Sodium Retention. Lancet **1:** 153 (Jan. 24), 1953.

Studies in 21 patients permitted description of three distinct changes: (1) primary water retention in the first 24 hours, (2) early sodium retention in the first 24 hours and (3) late sodium retention beginning 24 to 48 hours after operation and sometimes lasting several days. Potassium deficiency accen-

nated the third phase. From collateral data the authors suggest that the first phase is due to release of antidiuretic hormones as a result of emotion, trauma and drugs; that adrenocortical release plays a major role in the second and third phases; and that renal hemodynamic changes may contribute to the early water and sodium retention.

McKusick

Haxton, H. A.: Intra-aortic Blood Transfusion. Lancet **1:** 622 (March 28), 1953.

The author reviews the virtues of intra-arterial transfusion. Furthermore, he recommends direct intra-aortic transfusion by a left paraspinal approach at the level of the third lumbar vertebra. Experience in 20 cases is described. Spasm, thrombosis, and other complications to which peripheral arteries are prone when used for this purpose are avoided.

McKusick

Rammelkamp, C. H., Jr., and Weaver, R. S.: Acute Glomerulonephritis. The Significance of the Variations in the Incidence of the Disease. J. Clin. Investigation **32:** 345 (April), 1953.

It has been known for some time that there is an unpredictable variability in the occurrence of acute glomerulonephritis. A review of the literature demonstrates that the attack rate of acute nephritis following streptococcal infection varies from year to year and epidemics of nephritis are observed in family units or other population groups. It appears that the variations in the attack rates are due to varying nephritogenic capacities of the infecting organism. Observations during four years on a group of patients with acute nephritis in various cities show that type 12 streptococci were associated with 26 attacks. Four attacks were due to streptococcus type 4 and one to type 25. On the other hand, type 18 streptococci were isolated from two patients with nephritis in Hawaii. The data demonstrate that infection with type 12 and possibly type 4 streptococci is especially likely to be followed by an attack of acute glomerulonephritis, however, the data do not indicate the magnitude of the attack rate.

Because of the existence of nephritogenic strains of streptococci, the family or other group from which a patient comes should be observed for evidence of other apparent and nonapparent cases of the disease. If immunity to streptococcal infections in man is type-specific, the chances of developing a second attack of acute nephritis should be exceedingly small, since the number of streptococcal types responsible for nephritis is few.

Waife

AMERICAN HEART ASSOCIATION, INC.

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1954 HEART FUND CAMPAIGN

The annual Heart Fund campaign of the Association and its affiliates will be conducted throughout February, which has been designated Heart Month. This campaign is the principal source of financial support for the Association's program of scientific research, professional and lay education, and the development of community service programs. More than $8,500,000 was raised nationally in 1953 to support these aims.

"Help Your Heart Fund—Help Your Heart" will again be the slogan of the campaign. Heart Sunday, a fund-raising innovation first tested in Cleveland during the 1953 campaign, will be observed by a score of major cities and many smaller communities on February 14, St. Valentine's Day.

The National Office of the Association allocates at least one-half of its share of all funds raised to the furtherance of the national research program. Affiliated Associations also allocate substantial additional sums independently to support research programs in their areas.

Recognizing that public understanding of the scope of cardiovascular problems is indispensable to successful fund-raising and the expansion of the Heart Program, physicians increasingly render valuable support to the Heart Fund campaign in their localities. They serve as speakers and committee members, helping to inform the public on progress being made through research in the treatment and care of heart patients. Many assist in clinics, symposia and meetings devoted to the cardiovascular diseases, under sponsorship of the Association and its affiliates.

SECOND WORLD CONGRESS OF CARDIOLOGY

A booklet containing detailed information on the arrangements projected for the combined meeting of the Second World Congress of Cardiology and the Twenty-Seventh Scientific Sessions of the American Heart Association is available from L. W. Gorham, M.D., Secretary-General of the Congress, 44 East 23rd Street, New York 10, N. Y. The combined meeting will be held in Washington, D. C., Sept. 12–17, 1954, with opening ceremonies scheduled for Sunday, September 12.

As detailed by the booklet, the scientific program of the meeting will take three forms: (1) presentation of formal papers; (2) round table conferences dealing with important specific subjects such as hypertension, electrocardiography, coronary atherosclerosis, etc.; (3) clinical pathologic conferences. Papers may be presented in English, French or Spanish. Simultaneous translation facilities in these three languages will be provided for the round table conference meetings and for the clinical pathologic conferences. Scientific sessions will be held on Monday through Friday at the National Guard Armory. The booklet also describes the optional visits which delegates may make to the National Institutes of Health, the National Naval Medical Center at Bethesda, Md., the Army (Walter Reed) Medical Center and other institutions in Washington. Those who wish to see some of the more important university centers and cardiac clinics in the U. S. and Canada may participate in post-Congress tours, provided application is made in advance on a form provided in the booklet.

The booklet also contains an application blank for membership in the Congress and a hotel reservation form on which prospective visitors may indicate the type and price range of the accommodations they prefer. Membership fee for the Congress is $25.00, and includes all privileges, such as attendance at all Scientific Sessions, opening reception, formal banquet, special entertainments, local

medical sight-seeing tours, printed program, directory of registrants, Congress badge, etc. Associate Membership (wives and family) will cost $15.00 and include all privileges except the printed program.

Another form published in the booklet is designed for the convenience of those desiring to submit papers for the scientific program. American or Canadian physicians and others wishing to present papers are reminded that the deadline for titles with abstracts of not more than 200 words is April 1. These should be sent to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Contributors from countries outside the United States should submit titles with abstracts, which may be accompanied by translations in French, Spanish or German, to the Secretaries of their National Cardiological Societies as soon as possible, since the deadline for these to be received in the United States is March 1. These Secretaries will forward to the Secretary-General in New York only those titles and abstracts which have been approved by the Executive Committee of each National Society. Final selection will be made by the Program Committee on the basis of providing a well-balanced program.

Initial financial support for the organization of the Congress has been provided by the American Heart Association, the National Heart Institute of the United States Public Health Service and the Lasker Foundation. The Washington, D. C., Heart Association also is assisting in arrangements.

RESERVATIONS FOR AHA ANNUAL MEETING AND CLINICAL SESSIONS

Hotel reservations forms are now available from the American Heart Association, 44 East 23rd Street, New York 10, N. Y., for the convenience of those planning to attend the Annual Meeting and the special Scientific Sessions of the Section on Clinical Cardiology, scheduled to be held at the Conrad Hilton Hotel, Chicago, early in April. The Annual Meeting of the Assembly will be held Thursday and Friday, April 1–2; the special Scientific Sessions on Saturday and Sunday, April 3–4. Reservations should be mailed *directly* to the hotel in Chicago at the earliest possible date. The same hotel reservation form may be used by those desiring to attend both the meeting of the American Heart Association and that of the American College of Physicians which immediately follows.

The Scientific Sessions of the Section on Clinical Cardiology will be open to all members of the medical profession. Papers to be presented will be on subjects of distinct clinical interest. The deadline for receipt of abstracts expired Jan. 1, 1954.

ASSEMBLY PANELS FOR ANNUAL MEETING

The following have been appointed as chairmen to lead panel discussions at the Annual Meeting of the Association's Assembly, to be held in Chicago, April 1–2, 1954.

Panel I: LAY EDUCATION. . . . . George N. Aagaard, Jr., M.D., Dallas.
Panel II: PROFESSIONAL EDUCATION. . . . . J. Murray Kinsman, M.D., Louisville, Ky.
Panel III-A: HOME CARE. . . . . Martin Cherkasky, M.D., New York.
Panel III-B: CARDIAC IN INDUSTRY. . . . . Co-Chairmen: Richard J. Clarke, M.D., Boston; Lewis H. Bronstein, M.D., New York.
Panel IV: RESEARCH. . . . . Co-Chairmen: Eugene A. Stead, Jr., M.D., Durham, N. C.; Eugene B. Ferris, M.D., Atlanta, Ga.
Panel V: FUND RAISING. . . . . S. DeWitt Clough, Chicago.
Panel VI: RELATIONSHIPS BETWEEN NATIONAL, STATE AND LOCAL CHAPTER HEART ASSOCIATIONS. . . . . H. J. Smith, Arlington, Va.

WORLD LITERATURE ON BLOOD PRESSURE 1920–1950

A bibliography of World Literature on Blood Pressure (1920–1950) in three volumes has been collated under the direction of Earnest K. Koller and Jacob Katz, under the auspices of the Recess Commission on Hypertension of The Commonwealth of Massachusetts. Volume I contains an index of 16,460 references by authors. Volume II is an index of titles. Volume III contains approximately 1500 abstracts of papers pertaining to hypertension.

Price of the three volumes is $5.00. Sets may be purchased from the Public Document Di-

vision, office of the Secretary of the Commonwealth, Room 116, State House, Boston 33, Mass.

STAMFORD HEART ASSOCIATION LECTURE SERIES

The Stamford (Conn.) Heart Association has scheduled its second series of postgraduate cardiovascular lectures for physicians. The series, which has been accredited and endorsed by the American Academy of General Practice and the Stamford Medical Society, will be held on Tuesday evenings once each month through June at the Stamford Hospital Auditorium. A folder giving the detailed program may be had on request from the Stamford Heart Association, % Cardiac Clinic, Stamford Hospital, Stamford, Conn.

COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

A course in Electrocardiographic Interpretation for graduate physicians will be given at the Michael Reese Hospital by Louis N. Katz, M.D., Director of the Cardiovascular Department, Medical Research Institute, and associates. The class will meet each Wednesday from 7:00 to 9:00 p.m. for twelve weeks, beginning February 3. Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

NEW OFFICERS OF AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

At its recent annual meeting, the American Society for the Study of Arteriosclerosis elected the following officers for 1954: President, Russell L. Holman, M.D.; Vice-President, Louis N. Katz, M.D.; Secretary-Treasurer, O. J. Pollak, M.D. The next annual meeting will be held at the Sheraton Hotel in Chicago on Oct. 31–Nov. 1, 1954. Deadline for factual 300-word abstracts of papers for presentation at this meeting is May 31. Program Chairman is Arthur C. Corcoran, M.D., Cleveland Clinic, Cleveland, Ohio.

MEETINGS

Jan. 29–30: Western Society for Clinical Research, Seventh Annual Meeting; Portland, Ore.; Herbert N. Hultgren, M.D., Secretary-Treasurer, Stanford Hospital, San Francisco 15.

April 1–4: American Heart Association, Thirtieth Annual Meeting; Conrad Hilton Hotel, Chicago.

April 1–2: Assembly of the American Heart Association.

April 3–4: Scientific Sessions of Section on Clinical Cardiology of the Scientific Council, American Heart Association.

April 5–9: American College of Physicians; Conrad Hilton Hotel, Chicago; Mr. E. R. Loveland, Secretary, 4200 Pine Street, Philadelphia 4.

April 26–May 2: International Congress of International College of Surgeons, Sao Paolo, Brazil; Max Thorek, M.D., Secretary-General, 1516 Lake Shore Drive, Chicago.

May 17–19: American College of Surgeons, Sectional Meeting, London, England; Michael L. Mason, M.D., U. S. Secretary, 40 East Erie Street, Chicago 11.

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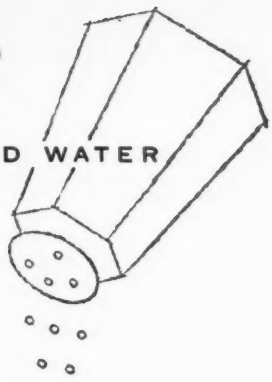

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